ANNULATIONS FROM CARBANIONIC PRECURSORS

A thesis presented by

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Contents

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Many thanks also go to my colleagues for their help and good humour and a special thanks to [redacted].

Lastly my thanks go to my parents for their constant support and encouragement.

Annulations From Carbanionic Precursors

Abstract

The work contained in this thesis is concerned with the generation and synthetic utility of dienolate anions and their derivatives. The research follows after the thesis presented in 1974 by Dr. T.W. Wallace of Imperial College and is developed from his research into the generation of dienolate anions from some β-alkyl-α,β-unsaturated ketones and esters and their reaction with benzynes.

A review of anthracyclinones is presented with emphasis being given to synthetic studies and to the preparation of semi-synthetic glycosides.

The use of 3-acyl and 3-carboxy-2-methylchromones as dienolate anion synthons has been examined and a new route to benzoxanthenones *via* an intramolecular annulation sequence is described.

A new route to substituted anthracenes from benzocyclobutenol and arynes is described.

A novel reaction of phthalide anion with Michael acceptors has been explored and the preparation of substituted 4-hydroxytetralones and 1-naphthols is described. The sequence has been extended by the use of substituted phthalide anions.

REVIEW

Anthracyclinones

Introduction

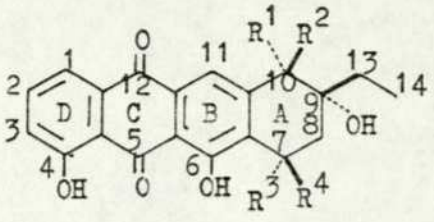
The constant need for new antibiotics has led to the screening of many hundreds of *Streptomycetes* species and this has revealed, amongst other compounds, the existence of numerous antibiotics - many of them being quinones. The anthracyclinones[1] form a major group of these pigments and are characterised by the 7,8,9,10 - tetrahydronaphthacene quinone system. They have been studied extensively by Brockmann and his co-workers[1] who found that they occurred both in the free form and, in combination with various sugars, including amino sugars, as glycosides (anthracyclines). Thus, after separation by countercurrent extraction and chromatography, the basic anthracyclines can be isolated as hydrochlorides or perchlorates.

As most of the anthracyclinones have different polyhydroxyanthraquinone chromophores, trivial nomenclatures were introduced, one of which was based on the orientation of the phenolic hydroxy groups. The individual members of *e.g.* the rhodomycinone series were arranged by Brockmann[1] according to the R_f values. The rhodomycinone of lowest R_f value was assigned the α- prefix. However, isolation of others with still lower values led to the α_1-, α_2- and α_3- subdivision.

All the anthracyclinones that have been isolated to 1978 are listed below. Their isolation and general structural elucidation have been reviewed.[2] Aklavinone (1), for example, was characterised as the triacetate, whose infra-red spectrum showed the presence of both phenolic and alcoholic acetates and an hydroxyl group (tertiary).

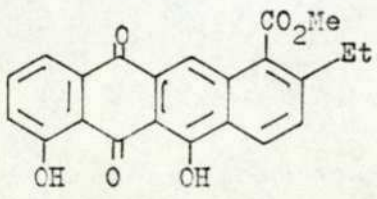
Spectral data and alkaline hydrolysis showed the presence of a methyl ester and the p.m.r. spectrum, an isolated ethyl group. The I.R. and U.V. - visible spectra were consistent with a 1,8-dihydroxyanthraquinone derivative. Acid-catalysed dehydration of (1) gave the bis-anhydroderivative having the spectral properties of a 1,11-dihydroxytetracene-5,12-quinone. The method used to determine ring A stereochemistry is discussed in the following section.

The Aklavinones



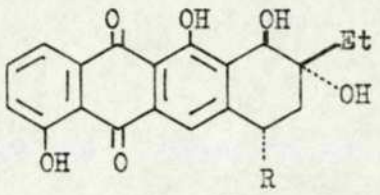
	R^1	R^2	R^3	R^4	
(1)	H	CO_2Me	OH	H	7S,9R,10R - Aklavinone
(2)	CO_2Me	H	OH	H	7R,9S,10R - Aklavinone I[3]
(3)	H	CO_2Me	H	OH	7R,9R,10R - Aklavinone II[3]
(4)	H	CO_2Me	H	H	9R,10R -7-deoxyalklavinone (galirubinone D)

(5)



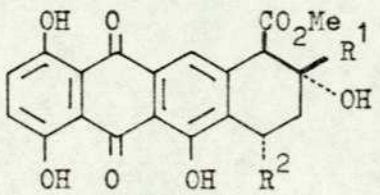
Bisanhydro-aklavinone (galirubinone B_1)

The Citromycinones

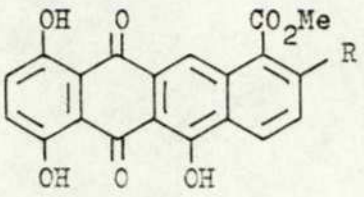


	R	
(6)	OH	7S,9R,10R-α-Citromycinone
(7)	H	9R,10R,-δ-Citromycinone

The Pyrromycinones

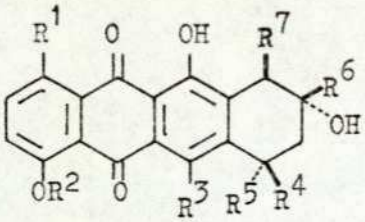


	R^1	R^2	
(8)	Et	OH	7S,9R,10R,-ξ-Pyrromycinone (rutilantinone)
(9)	Me	OH	7S,9R,10R,-ξ_1-Pyrromycinone[4]
(10)	Et	H	9R,10R,-ζ-Pyrromycinone (galirubinone C)



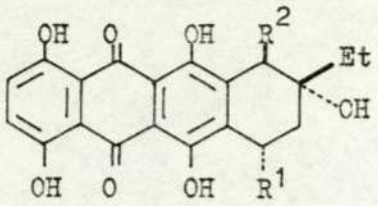
	R	
(11)	Et	n-Pyrromycinone (galirubinone B_2, ciclacidine)
(12)	Me	n-Pyrromycinone

The Rhodomycinones



	R^1	R^2	R^3	R^4	R^5	R^6	R^7	
(13)	H	H	OH	OH	H	Et	OH	A-Rhodomycinone
(14)	OH	H	H	H	OH	Et	OH	α_2-Rhodomycinone
(15)	H	H	OH	H	OH	Et	OH	β-Rhodomycinone
(16)	H	H	OH	H	H	Me	OH	β_1-Rhodomycinone
(17)	H	H	OH	H	H	Et	OH	γ-Rhodomycinone
(18)	H	H	OH	H	H	Et	H	10-deoxy-γ-Rhodomycinone
(19)	OH	H	H	H	OH	Et	CO_2Me	δ-Rhodomycinone
(20)	H	H	OH	H	OH	Et	CO_2Me	ε-Rhodomycinone
(21)	H	H	OH	H	H	Et	CO_2Me	ζ-Rhodomycinone
(22)	H	Me	OH	H	OH	Ac	H	Daunomycinone
(23)	H	Me	OH	H	OH	$COCH_2OH$	H	Adriamycinone
(24)	H	H	OH	H	OH	Ac	H	Carminomycinone[5]

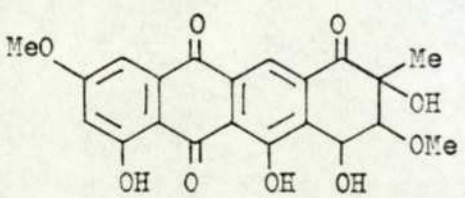
The Isorhodomycinones



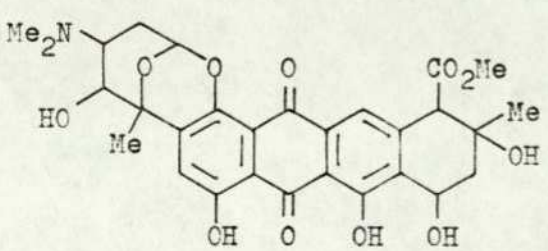
(25)	OH	OH	β -Isorhodomycinone
(26)	H	OH	γ -Isorhodomycinone
(27)	OH	CO_2Me	ε -Isorhodomycinone
(28)	H	CO_2Me	ζ -Isorhodomycinone

Other Anthracyclinones

(29) Steffimycinone[6]

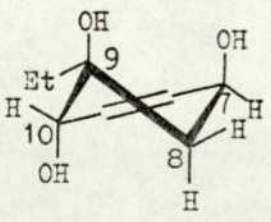


(30) Nogalarol[7]

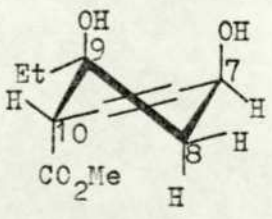


Stereochemistry of the Anthracyclinones

According to Brockmann and Legrand[8] the circular dichroism (c.d.) curve in the region 270 - 390 n.m. depends on the ring A substitution and stereochemical pattern and not on the orientation of the phenolic hydroxy groups. They found that all the curves had a similar characteristic S-shape; the dichroism is very large and is chiefly affected by the asymmetric centres at C-10 and C-7, and as C-9 is further from the chromophore, it has relatively little effect. Introduction of a further asymmetric centre at C-9 to derivatives possessing asymmetry at C-10 always increases the amplitude of the c.d. curve, thus indicating that the configuration at C-9 is always the same. The amplitude is considerably increased, however, by almost the same amount in each case when a third asymmetric centre at C-7 is present, and, since the $\Delta\varepsilon_{max}$ value is almost doubled, the substituents at C-10 and C-7 must have the same steric relationship to the chromophore and so must be mutually trans. The hydroxyl groups at C-9 and C-10 in α-rhodomycinone (17) have a trans-relationship (reluctance to react with periodate) and the ring A stereochemistry is shown in (31).



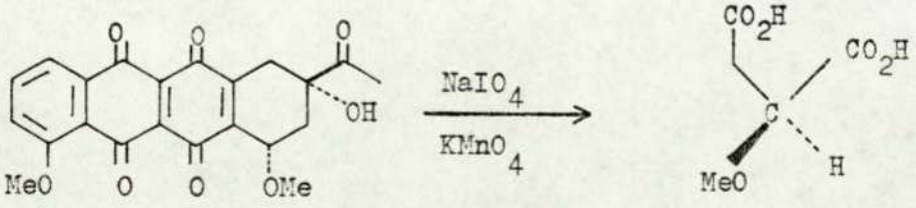
(31)



(32)

The following conclusions were drawn for pigments having a carbomethoxy substituent at C-10. Pyrolytic formation of anhydroderivatives proceeds by cis-elimination of water, therefore, for example in ε-pyrromycinone (10), the hydroxyl at C-9 is cis to the proton at C-10. Also as ε-rhodomycinone and ε-isorhodomycinone tetramethyl ethers form isopropylidine derivatives with acetone dimethyl ketal, the hydroxyls at C-9 and C-7 must be cis to each other. In the light of those considerations the arrangement (32) was proposed. Not only do the conformations (31) and (32) gain stability via the intramolecular hydrogen bonding between the cis-diaxial hydroxyl groups but also because the ethyl group occupies a psuedoequatorial position.

In 1968 Arcamone and co-workers[9] reported the absolute stereochemistry of daunomycinone (22). It was determined as follows. Oxidation of the 7-O-methyl derivative (prepared by partial demethylation of daunomycinone trimethyl ether with aluminium chloride in benzene) with lead tetra-acetate gave the diquinone (33) which, without isolation, was further oxidised (permanganate-periodate)[10] to give S(-)methoxy-succinic acid (34). Therefore C-7 has the S-configuration and since (22) forms an isopropylidene derivative, the hydroxyls at C-9 and C-7 have a cis relationship and so C-9 was also assigned the S-configuration.

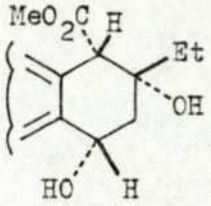


(33) (34)

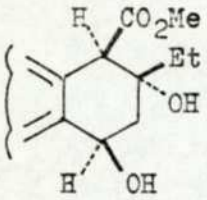
Scheme 1

Thus, by correlation of the c.d. curve of both daunomycinone (22) and the 7-deoxy derivative,[11] it was possible to show[12] that ε-pyrromycinone (8) and several other anthracyclinones also have the (7S)-configuration. The use of p.m.r. data, chemical relationships and comparison of c.d. curves gave the absolute configurations of the majority of the anthracyclinones previously illustrated.[12]

Recently Tresselt and his co-workers[3] have used the above techniques to assign the absolute configuration of two new aklavinones, I(2) and II(3), and it is interesting to note that aklavinone I(2) is the first anthracyclinone to have a c.d. curve of opposite sign.



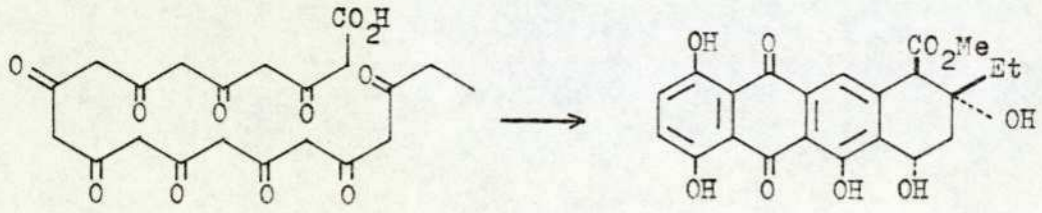
(2)



(3)

Biosynthesis

Quinones are derived from a few key intermediates by a series of reactions which lead to the formation of benzenoid compounds. It is probable that most quinones arrive from the acetate - malonate pathway. Anthracyclinones, however, appear to be formed from nine acetate units and one propionate unit. In the early sixties Ollis and co-workers[13] proposed the pathway shown in Scheme 2 for the biosynthesis of ε-pyrromycinone (8). Radioactive (8) (0.6% incorporation) was obtained by the addition of $CH_3{}^{14}CO_2Na$ to a rutilantin culture and the results of the degradation studies showed that nine acetate units were incorporated into the molecule. Similarly, the use of carboxy-labelled sodium propionate showed the incorporation of one propionate unit. The biosynthetic scheme leading to (8) was one of the first examples of a mixed acetate-propionate biosynthesis.

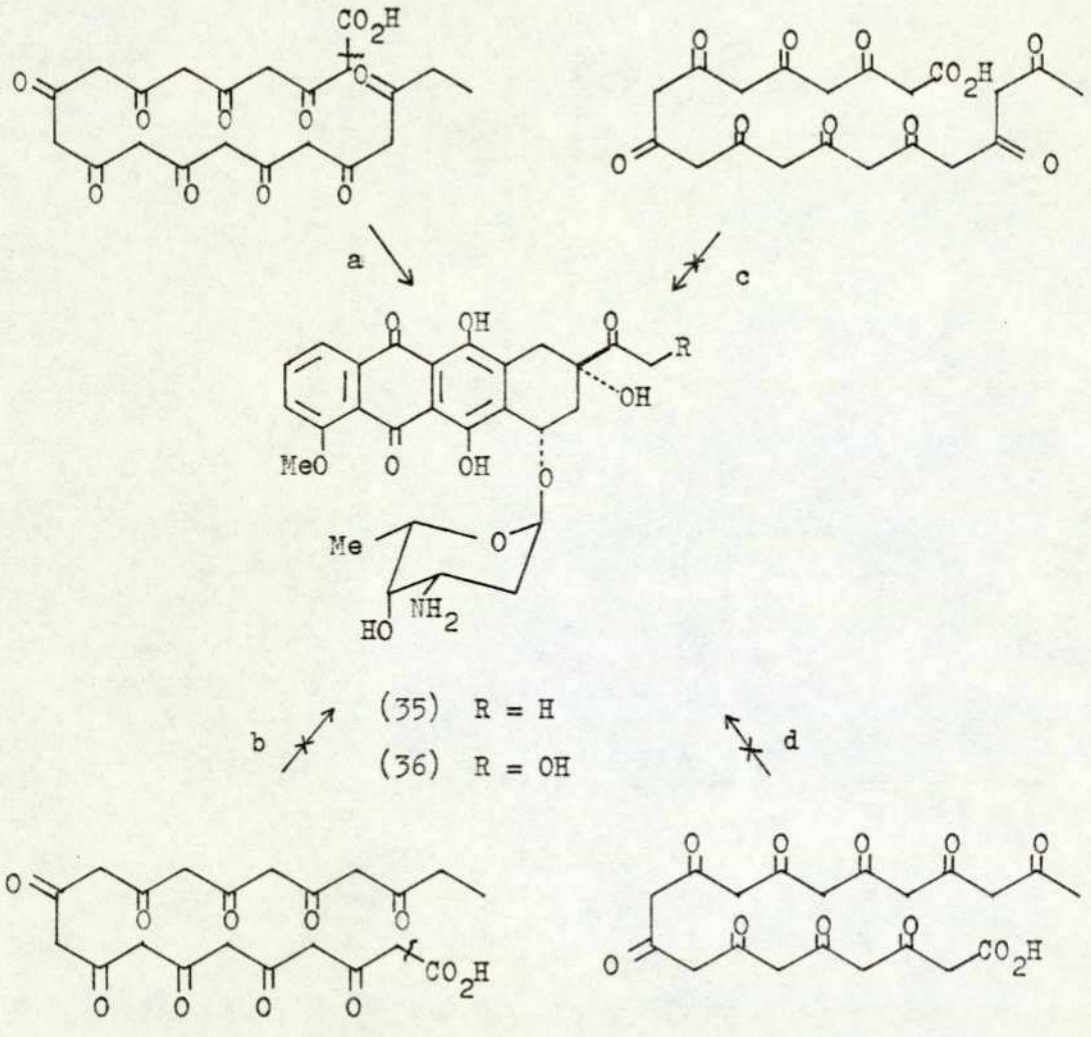


(8)

Scheme 2

Using the more modern technique of ^{13}C n.m.r. spectroscopy Whitlock and his co-workers[14,15] studied the biosynthesis of daunorubicin (35) from $^{13}CH_3{}^{13}CO_2Na$. For the carbon n.m.r. studies crude daunorubicin (35) was hydrolysed and acetylated to give daunomycinone tetra-acetate (37). There are a number of plausible biosynthetic routes to (35), viz an acetate-polymalonate route (c or d) or a propiolate-polymalonate route (a or b) (Scheme 3).

Incorporation of sodium $[1-^{13}C]$ and $[2-^{13}C]$ acetate into daunorubicin gave the labelled tetra-acetates (37) from which it was clear that the biosynthesis of daunorubicin (35)* did not conform to a "classical" acetate-polymalonate pathway (pathway c or d).



Scheme 3

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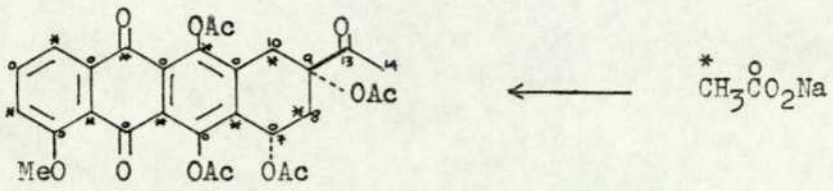
* Daunorubicin is now the preferred name. In early literature (35) was known as daunomycin. Daunomycinone (22) is the aglycone of (35).

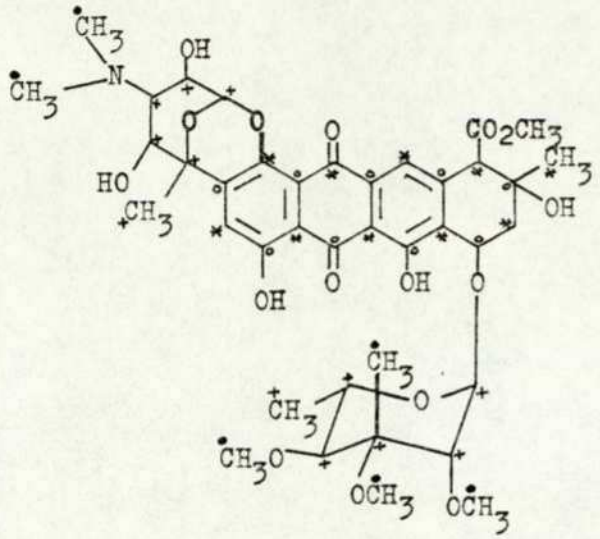


(37)

Scheme 4

The ^{13}C n.m.r. spectrum of (37) derived from doubly-labelled sodium acetate confirmed that the three-carbon fragment [9,13,14] was not acetate derived and showed that carbons 7 and 8 were derived from the same unit whereas carbon 10 was a singlet. This conclusion uniquely requires path a (Scheme 3); a propionate "starter" unit and nine successive malonate condensations with loss of the terminal carboxyl group.

The biosyntheses of nogalamycin (38) and steffimycin B (39) have also been studied using ^{13}C n.m.r. spectroscopy.[16] Not only were $CH_3{}^{13}CO_2Na$ and $^{13}CH_3CO_2Na$ added to the fermentations, but also $^{13}CH_3$-labelled methionine and uniformly ^{13}C labelled glucose, in order to study the incorporation of one carbon units and the sugar biosynthesis. The results, shown in Figure 1, clearly show that the aglycones of nogalamycin (38) and steffimycin B (39) arise from ten acetate units starting from the C-9 methyl groups and that the neutral sugars are derived from glucose, while CH_3O and CH_3N methyl groups come from methionine.



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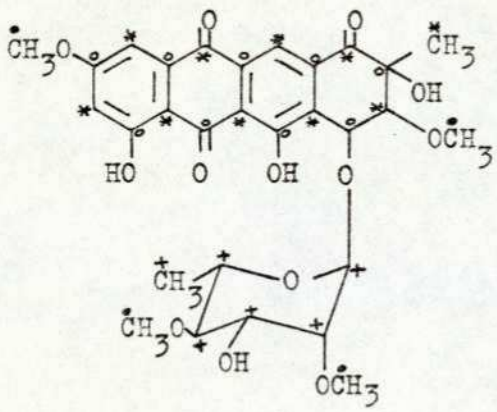


(39)

$^{*}CH_3\overset{\circ}{C}O_2Na$ + D-Glucose . CH_3 of methionine

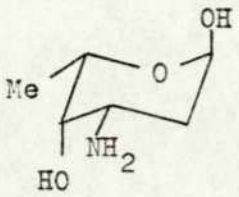
Figure 1 Origin of the various carbon atoms in Nogalamycin (38) and Steffimycin B (39)

Synthetic Studies towards Anthracyclinones

Over the past twenty five years many antibiotics which contain a linear tetracyclic skeleton have been isolated from different kinds of bacterial cultures. Owing to their intriguing structures and their potent antibacterial properties, the tetracyclines gained the attention of many organic chemists and syntheses of this group of antibiotics have been reported by many research groups.[17] Although the rhodomycins are another group of antibiotics having a linear tetracyclic skeleton, they are not as active against bacteria as the tetracyclines. Subsequently two members of the group, daunorubicin (35) and adriamycin (36) were isolated and found to be highly active against certain tumours.[18] They have become established antineoplastic agents used for the clinical treatment of a broad spectrum of human cancers, but the principle limit on their utility is their high cardio-toxicity (especially daunorubicin (35)).[19] This fact coupled with an inefficient biosynthetic process for its production,[22] has stimulated considerable work on the total synthesis of these compounds and their analogues.

On mild acid hydrolysis the anthracyclines (35) and (36) give the aglycones, daunomycinone (22) and adriamycinone (23) and the aminosugar daunosamine (40). As the coupling of sugar groups to aglycones is possible (see page 56), the synthetic studies were directed towards the preparation of the aglycones (ie (41)).

There have been many different approaches to the synthesis of these types of compounds and they can be divided into two annulation sequences, BA ⟶ DCBA and DCB ⟶ DCBA.



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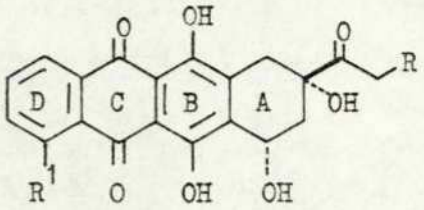
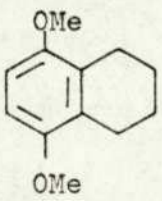


(41)

BA→DCBA Sequence

In 1968 Goodman and co-workers[11] reported the synthesis of compound (49), a tetracyclic analogue of daunomycinone (22) and, also, its conversion to the D-glycoside. Their method was to condense the dimethoxytetralin (42) with the mixed anhydride of methyl hydrogen phthalate and trifluoroacetic acid to give, in excellent yield, the keto-ester (43), which was saponified to the acid (44).



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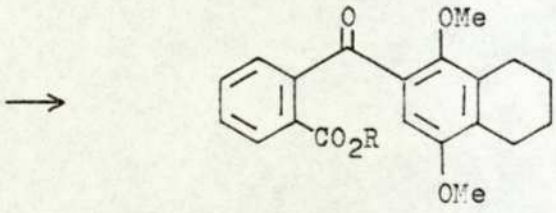
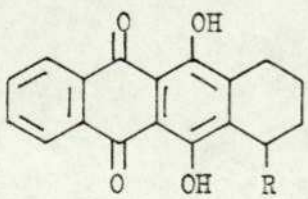


(43) R = Me

(44) R = H



(45) R = H

(46) R = Br

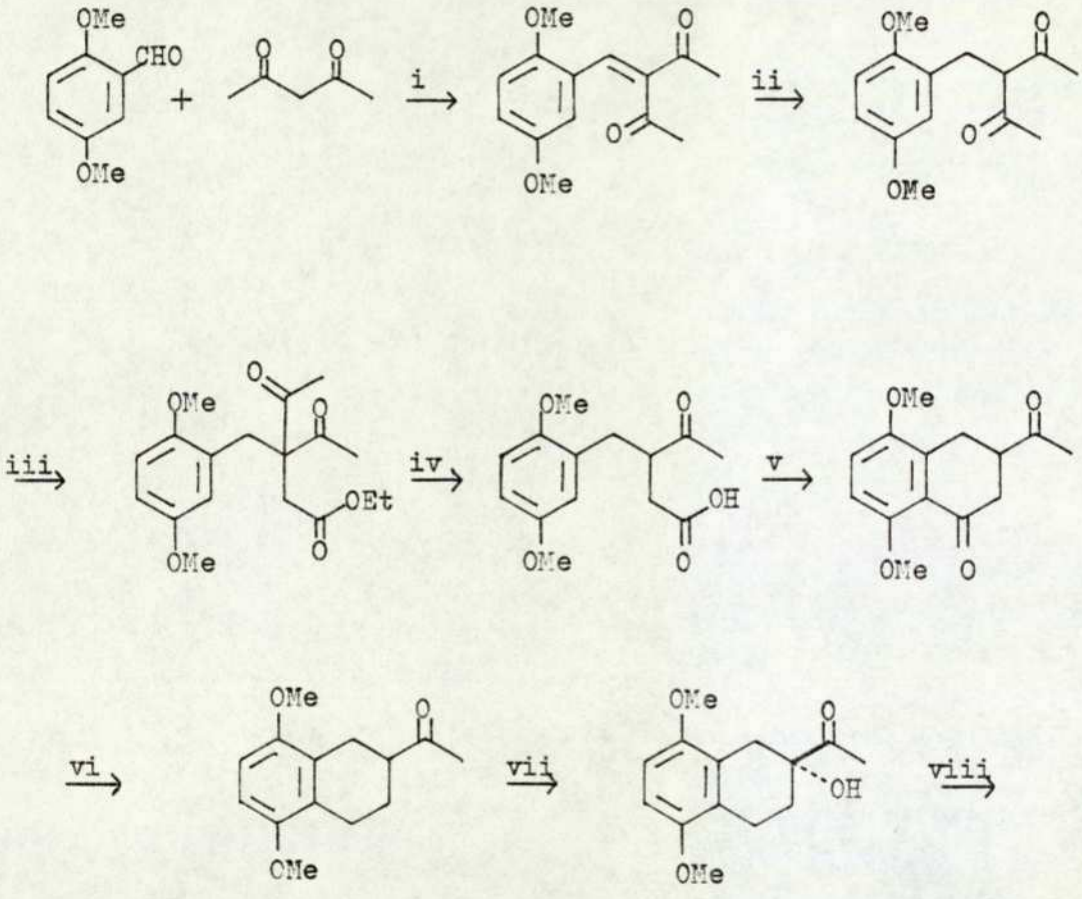
(47) R = OCOMe

(48) R = $OCOCF_3$

(49) R = OH

Ring closure (sulphuric acid) and demethylation ($AlCl_3$) to (45), followed by bromination gave (46) which, on treatment with silver acetate, gave *inter alia*, (47). Attempts to convert (47) directly to (49) were unsatisfactory but the conversion was accomplished *via* the trifluoroacetate (48).

Scheme 5



(50)

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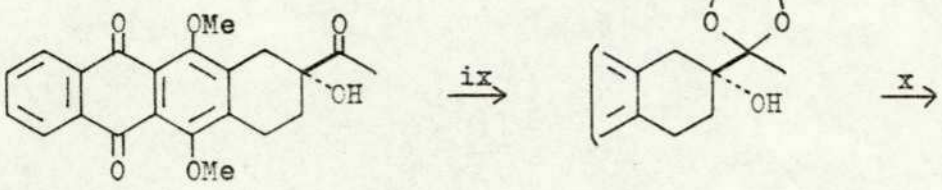
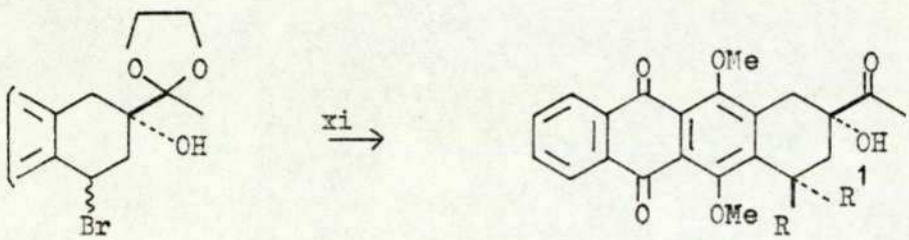
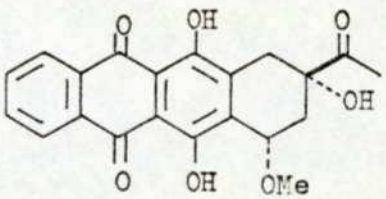


(51) (52)



(53) (54) R = OMe, R^1 = H

(55) R = H , R^1 = OMe



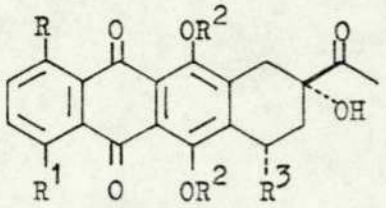
(56)

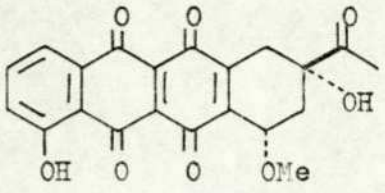
Reagents: i, AcOH, piperidine benzene; ii, EtOH 5% Pd/C; iii, NaH, $BrCH_2CO_2Et$, THF; iv, $NaOH/H_2O$; v, HF; vi, $H^+/EtOH$, 5% Pd/C; vii, Bu^tOH, $KOBu^t$, O_2 then Zn; viii, Phthalic acid monomethyl ester, trifluoracetic anhydride, then $NaOH/H_2O$ then, HF; ix, $HOCH_2CH_2OH$, TsOH, benzene; x, NBS, CCl_4, Δ; xi, anhydrous MeOH, Δ; xii, AlCl , benzene.

In the initial approach towards the synthesis of daunomycinone Wong and his co-workers[23] used as the BA ring system the substituted tetralin (50), prepared in a seven step procedure from 2,5-dimethoxybenzaldehyde (Scheme 5). (50) was easily condensed with phthalic acid monomethylester and the product hydrolysed and cyclised to the tetracyclic hydroxyketone (51). Bromination of the ensueing ketal (52) gave a mixture of unstable bromides, which, without purification, were heated at reflux temperature in anhydrous methanol to give, inter alia, (54) and (55). (55) was then demethylated to 4-demethoxy-7-O-methyl daunomycinone (56).

Having successfully prepared (56), Wong[24] adapted the procedure to the preparation of daunomycinone (22) itself, but was unable to obtain a regiospecific procedure. Again the substituted tetralin (50), (prepared via an improved procedure) was the starting BA system. This time it was condensed with 3-acetoxyphthalic acid monomethyl esters (isomeric mixture), and in the same sequence as before, gave the quinones (57) and (58), which were quantitatively methylated to (59) and (60). Separation of the mixture was not possible at this stage and it was then sequentially ketalized, brominated at C-7, methanolysed and hydrolysed to give the trimethyl ethers (61) and (62) which could be separated by preparative t.l.c. To complete the synthesis of daunomycinone (22), (61) was demethylated with aluminium chloride to give (62) which was oxidised (lead tetra-acetate) to the unstable diquinone (64) and immediately remethylated and reduced to give racemic 7-O-methyldaunomycinone (65) in low yield. Replacement of the benzylic methoxy group with a trifluoroacetoxy group resulted in (66) which, when treated with ammonium hydroxide in boiling

acetone, afforded racemic daunomycinone (22) in an overall yield of < 1%.





(64)

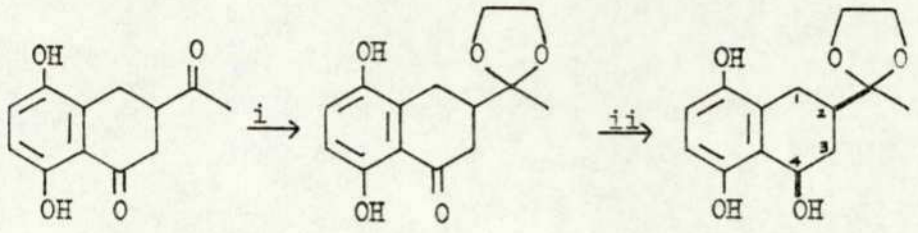
	R	R^1	R^2	R^3	
(57)	H	OH	Me	H	
(58)	OH	H	Me	H	
(59)	H	OMe	Me	H	
(60)	OMe	H	Me	H	
(61)	H	OMe	Me	OMe	
(62)	OMe	H	Me	OMe	
(63)	H	OH	H	OMe	
(65)	H	OMe	H	OMe	
(66)	H	OMe	H	$OCOCF_3$	(epimer)
(67)	OMe	H	H	OH	

Parallel experiments performed on the iso-derivative (62) gave racemic iso-daunomycinone (67). It is interesting to note that a similar synthesis has recently appeared in the patent literature[25]. Racemic (50) was resolved to give (-) (50), which now has the natural configuration at C-2. Acylation with various phthalic mono-esters followed by cyclisation afforded the required tetracyclic system.

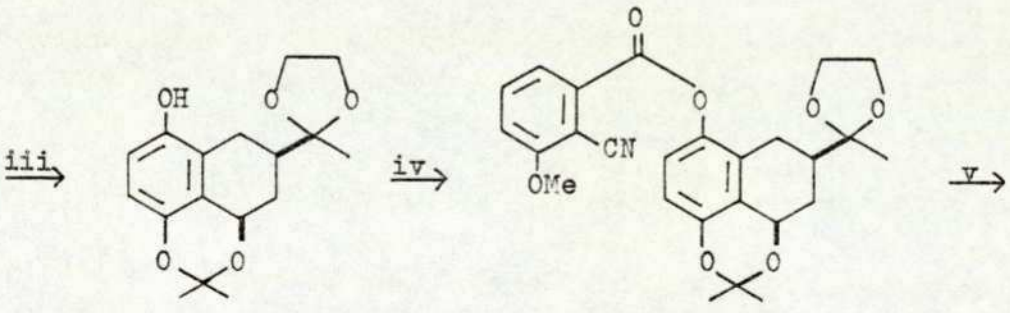
These synthetic schemes reflect one of the major difficulties with the preparation of the aglycones, namely the need to control regiospecificity in the construction of the tetracyclic ring system. Kende and co-workers[26] have reported a short, mild and completely regiospecific procedure (Scheme 6) which resulted in the first total synthesis of (±)-9-deoxydaunomycinone (75). The key reaction which maintained regiospecificity was the photochemical Fries rearrangement of the o-cyanobenzoate ester (72). Reduction of the ketal (69) with sodium borohydride gave the cis-orientated trihydroxy ketal (70) (83%) by attack of hydride from the less hindered side. This was converted to the highly sensitive ketal acetonide (71). The free phenol of (71) was acylated to give the key intermediate (72). The stereochemistry about C-4 for compounds (70), (71) and (72) could be assigned on the basis of their p.m.r. spectra. Analysis of the benzylic -CH(OR)- proton revealed, in each case, the X signal of an ABX quartet with J_{AX} = 12 Hz and J_{BX} = 4 Hz, requiring a pseudoequatorial orientation of the benzylic oxygen in each of the intermediates. The ketal substituent at C-2 would also have the same orientation, and these observations are in agreement with the known preference[12] of large β-substituents in tetralin systems to adopt the equatorial conformation.

The photolysis of (72) could not be continued to completion, since over-irradiation resulted in destruction of the product (73). The optimum yield of (73) was 48% together with a 47% recovery of starting material. The hindered cyano group was then hydrolysed with aqueous base to give the acid (74), still containing the acetonide and ethylenedioxy groups (p.m.r. analysis). Finally, treatment of (74) with liquid hydrogen

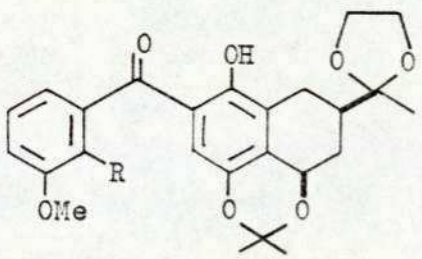
Scheme 6



(68) (69) (70)



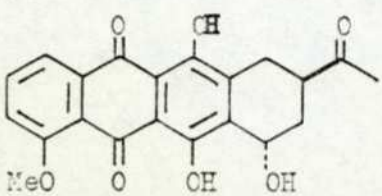
(71) (72)



(73) R = CN

↓ vi

(74) R = CO_2H vii →



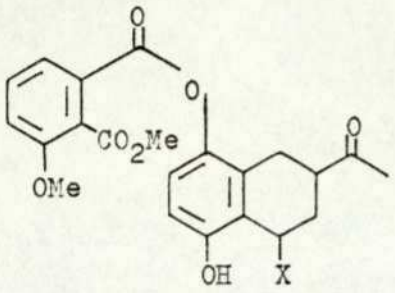
(75)

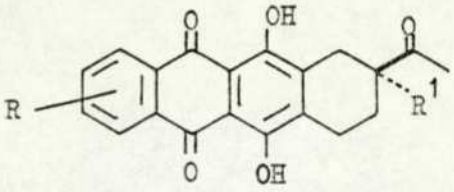
Reagents i, $HOCH_2CH_2OH$, TsOH, benzene, ii, $NaBH_4$, THF; iii, 2,2-dimethoxypropane, TsOH; iv, 3-methoxy-2-cyanobenzoic acid; v, $h\nu$, dioxane; vi, 10% NaOH, Δ, N_2; vii, HF.

fluoride, followed by pouring the reaction mixture into a -60° mixture of chloroform and sodium carbonate solution gave the anthracyclinone (75) in 25% yield. The structure and stereochemistry was unamibuously confirmed by comparison of the p.m.r. spectra of (75) and daunomycinone (22). The benzylic proton of (75) shows a narrow multiplet ($W_{\frac{1}{2}}$ = 5 Hz)* at δ5.24 corresponding to that observed at δ5.33 ($W_{\frac{1}{2}}$ = 7 Hz) in natural daunomycinone. For other anthracyclinones epimeric at C-7, the corresponding signal widths have values of 13-17 Hz,[27] thus indicating that the C-7 proton of (75) does have a pseudoequatorial orientation.

In a parallel synthesis Sih et al[28] reported the preparation of (±)-7-deoxydaunomycinone (82). They also used the dihydroxytetralone (68), and, because of hydrogen-bonding between the carbonyl and the adjacent phenolic group, they were able to acylate (68) with 2-carbomethoxy-3-methoxybenzoic acid to give the diester (76). Attempts to catalyze a Fries-rearrangement and subsequent dehydrative cyclization, by treating (74) with boron trifluoride etherate, led only to small amounts of tetracyclic compounds. Similar results were obtained with the alcohol (77). With (78) (from hydrogenolysis of (76)), however, a 37% yield of an isomeric mixture of the cyclized products (79) and (80) were obtained. In this sequence the Lewis-acid catalysed cyclization did not proceed regiospecifically. Attempts to correct this deficiency by alkylating the phenol (78) and repeating the reaction were unsuccessful. The only redeeming feature of this work was the novel way in which the tertiary hydroxyl group at C-9 was introduced into compound (80). This was accomplished in 50% yield by enol acetylation of (80), followed by epoxidation and hydrolysis to afford (±)-7-deoxydaunomycinone (82). (79) was similarly transformed into the iso-derivative (81).

*$W_{\frac{1}{2}}$ - peak width at half peak height quoted as $W_{\frac{1}{2}}$ values in Hz.





(76) X = =O

(77) X = OH

(78) X = H

(79) R = OMe at C-1 R^1 = H

(80) R = OMe at C-4 R^1 = H

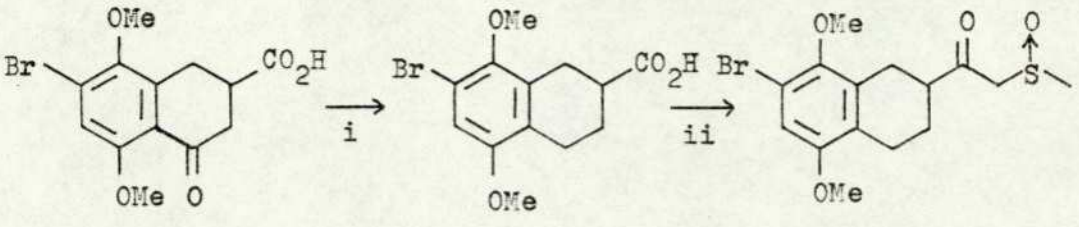
(81) R = OMe at C-1 R^1 = OH

(82) R = OMe at C-4 R^1 = OH

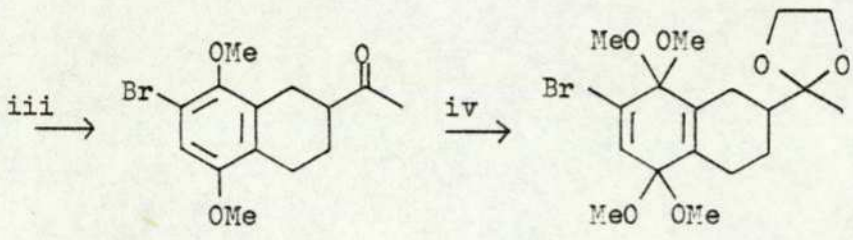
A regiospecific procedure for the coupling of the BA-ring fragment of the aglycone to dimethyl 3-methoxyphthalate (89) has recently been reported by Reynolds and co-workers.[29] Their synthetic approach was based on the observation that an appropriate organometallic reagent selectively attacks one of the carbonyl groups of the phthalate (89) (Scheme 7).

The acid (84) was converted into the bromo-compound (87) which on treatment with n-butyl lithium afforded the lithio-derivative (88). This was regiospecifically coupled with the phthalate (89) in good yield. The conversion of compound (90) to the tetracyclic system (91) was accomplished in 40% yield without isolation of the intermediates.

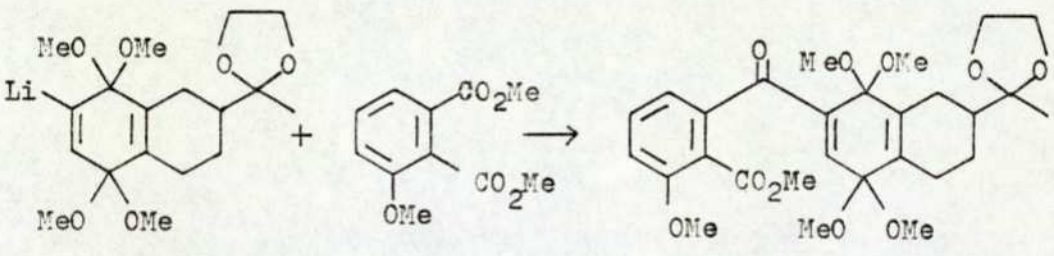
Whilst the 9-hydroxy substituent can be readily introduced into compound (91)[28], the methods available for the reintroduction of the 7-hydroxy function[30,31,32] are not suitable for large-scale reactions.



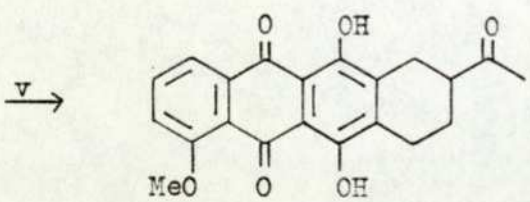
(83) (84) (85)



(86) (87)



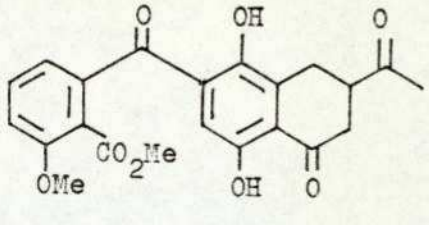
(88) (89) (90)



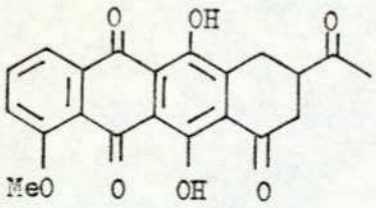
(91)

Scheme 7 Reagents: i, Et_3SiH, TFA; ii, a) CH_2N_2, b) $CH_3S(O)CH_2Li$; iii, Al(Hg); iv, a) $HOCH_2CH_2OH$, H^+, b), electrolysis, MeOH; v, a) TFA, H_2O, $SnCl_4$, b) OH^-, c) HF.

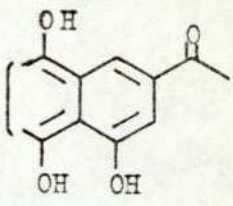
(The authors anticipated requiring 10-20g of (±) daunomycinone for resolution and analogue studies). In an attempt to retain the latent 7-hydroxyl functionality of the ketone (83), the sequence was repeated retaining the keto-group. Thus (83) was transformed into the benzophenone (92), which on cyclisation afforded a mixture of the ketone (93) and its oxidation product (94). Attempts to obtain (93), free of (94) were unsuccessful and the lability of the ketone (93) precluded its use in any further transformations.



(92)



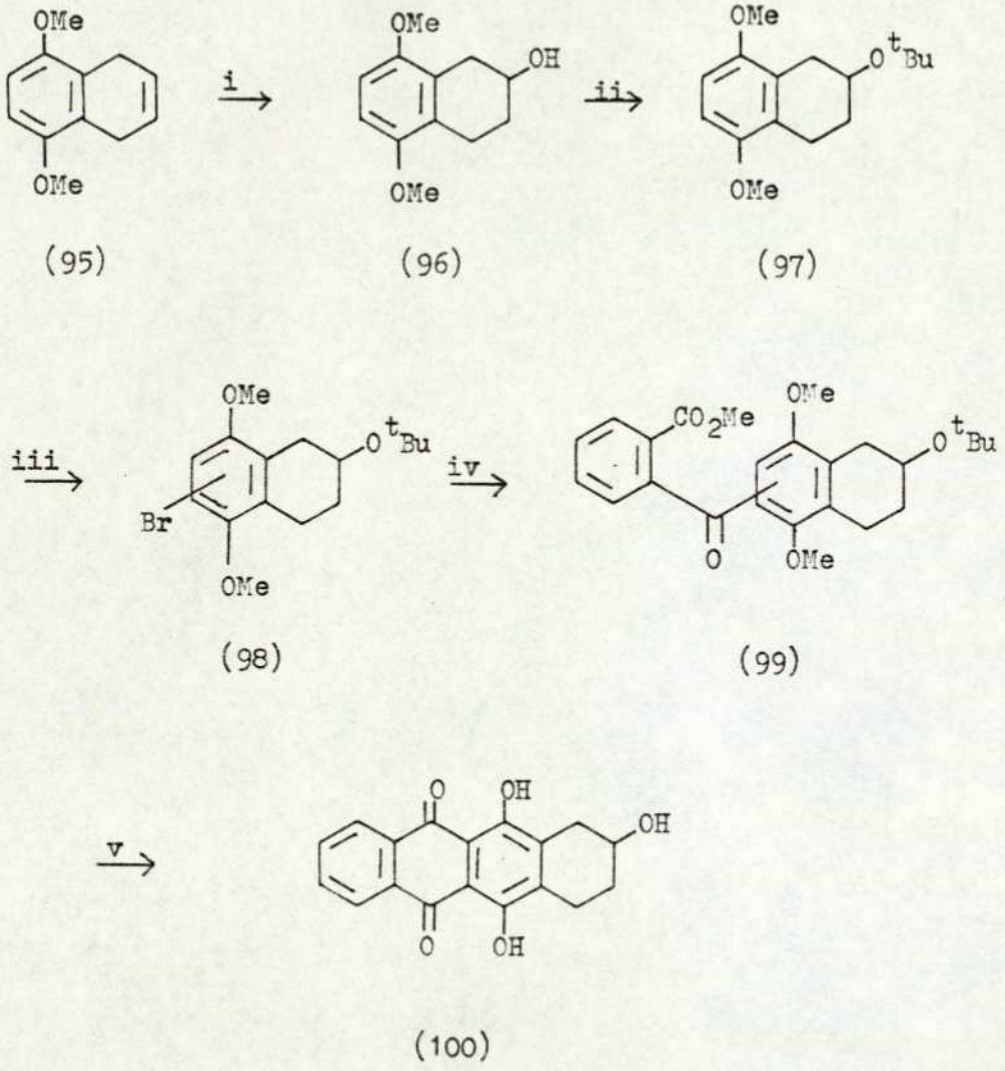
(93)



(94)

A lower yield of the tetracyclic system (91) was obtained when the sequence was repeated with the aryl lithium species derived from (86) in place of the protected quinone anion (88). Even so, the aryl lithium approach would serve as a viable alternative route to anthracyclinones. Interesting features of the scheme are that the sequence involved only one chromatographic separation and that alkylation of the β-keto-sulphoxide (85) would allow the preparation of side-chain analogues.

Scheme 8

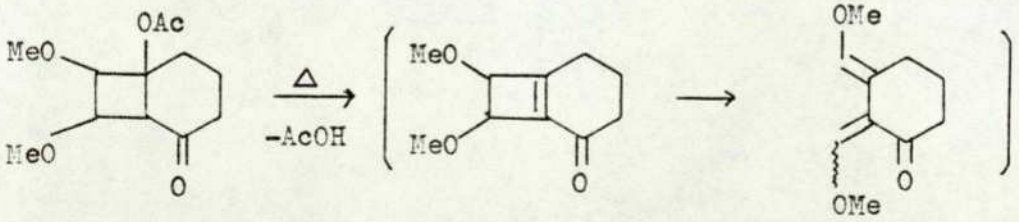


Reagents: i, i) B_2H_6, ii), H_2O_2, OH^-; ii, $BF_3.Et_2O$, H_3PO_4, isobutylene; iii, Br_2, $CHCl_3$; iv, -100°, nBuLi, THF, dimethylphthalate; v, a) DCM, BCl_3, b) 0.5N HCl

In a more recent communication Mitscher and Alexander[33] have described a short synthesis of an anthracycline synthon using an aryl lithium procedure (Scheme 8). Treatment of the bromides (98) with n-butyl lithium, followed by dimethyl phthalate afforded the esters (99) (65%) which then underwent cyclization and deprotection to give the alcohol (100) in nearly quantitative yield. The oxidation of the alcohol (100) to the corresponding ketone[34] and transformations of the compounds into aglycones have been reported[32] (see page 46). It should be possible to extend this sequence to the preparation of more highly functionalized synthons.

In the preparation of aglycones, many chemists utilized the Diels-Alder reaction in a DCB ⟶ DCBA ring - forming sequence. However two groups have incorporated this reaction into the BA ⟶ DCBA sequence using novel strategies.

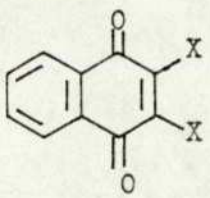
The sequence, developed by Boeckmann et.al,[35] involves the thermolysis of a cyclobutane which eliminates acetic acid and undergoes ring-opening to give a butadiene (e.g. (103) Scheme 9), which is trapped with a dienophile to give a linear polycyclic aromatic system.



(101) (102) (103)

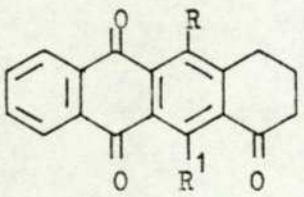
Scheme 9

The most useful diene precursor was found to be the acetate (101). Thus treatment of (101) in 2-dichlorobenzene (180°, 3 hrs.) with 1,4-



(104a) X = H

(104b) X = Cl



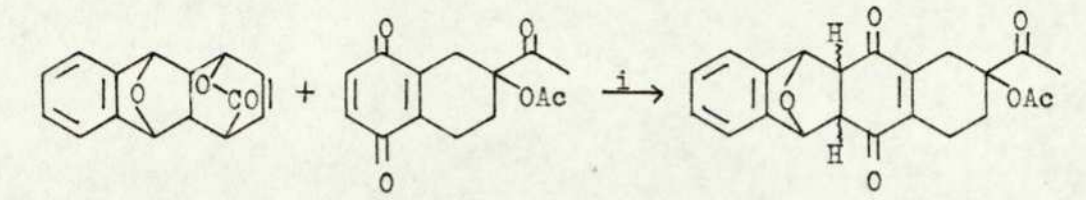
(105) R = R^1 = H

(106) R = R^1 = OMe

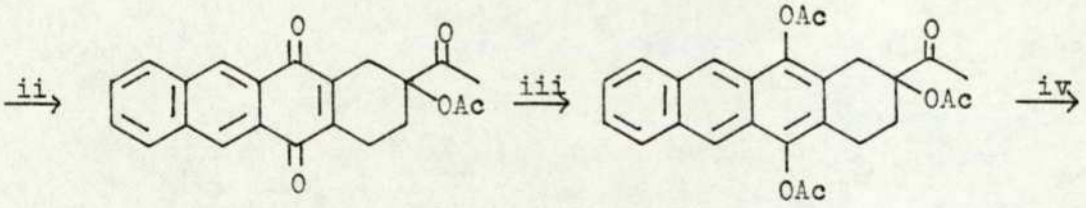
(107) R = OMe, R^1 = H

naphthoquinone (104a) gave a 60% yield of the tetracyclic system (105). In an attempt to obtain the 6,11-dimethoxy derivative (106), the dichloro compound (104b) was used as the dienophile. Surprisingly, the only isolated product was the ketone (105). In an attempt to induce elimination of HCl from the initial Diels-Alder adduct the reaction was repeated in the presence of lithium carbonate. This afforded the monomethoxy derivative (107) in moderate yield. This disappointing result rather limits this interesting sequence.

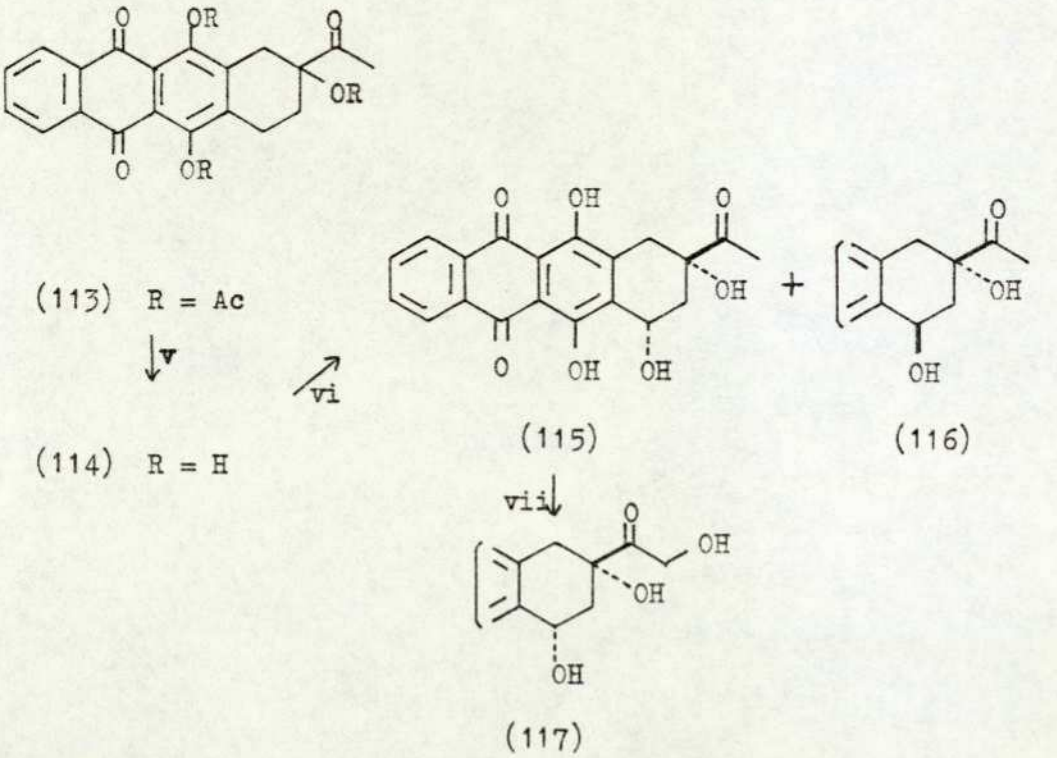
A completely new approach to the construction of the anthracyclinone skeleton has been reported by Kende et.al[36]. The sequence (Scheme 10) involves addition of a C_8 isobenzofuran unit to the quinone form of a preformed AB synthon.



(108) (109) (110)



(111) (112)



(113) R = Ac

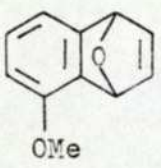
(114) R = H

(115) (116)

(117)

Scheme 10 Reagents: i, 140°, diglyme; ii, NaOAc, AcOH, Δ ; iii, Zn, Ac_2O; iv, CrO_3, AcOH; v, 6N HCl-AcOH, 70° vi, a), Br_2, CCl_4, AIBN, Δ , b), AgO_2CCF_3, c), H_2O; vii, a), Br_2, $CHCl_3$, b), 0.002M NaOH, 80% acetone, 60°

Thermolysis of the lactone (108) (prepared by the reaction of the benzyne-furan adduct with α-pyrone) in the presence of the bicyclic quinone (109) (prepared from 1,4-dimethoxy-6-tetralone, c.f. Scheme 16) afforded a mixture of the endo and exo adducts (110) (96%). Aromatization of the mixture to the quinone (111), followed by reduction to the triacetate (112) and C-ring oxidation afforded the quinone (113), which was hydrolysed to give the hydroxyketone (114). C-7 functionalisation using methods developed in previous syntheses[37] (Scheme 16) afforded a mixture of the alcohols (115) and (116), which, after equilibration with trifluoracetic anhydride followed by methanolysis, gave racemic 4-demethoxydaunomycinone (115) in 45% yield from (113). Conversion to (±)-4-demethoxyadriamycinone (117) was achieved using known procedures.

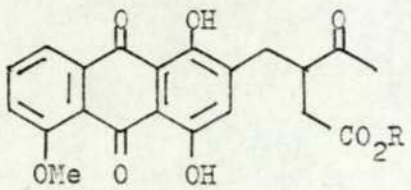


(118)

The process, however, lacks regiospecificity as repeating the sequence with the 3-methoxybenzynefuran adduct (118) afforded an inseparable mixture of (±)-7-deoxydaunomycinone and its 1-methoxy counterpart. Even so, the new strategy provides an efficient convergent route to the aglycone system and compares favourably with existing sequences.

DCB→ DCBA Sequence

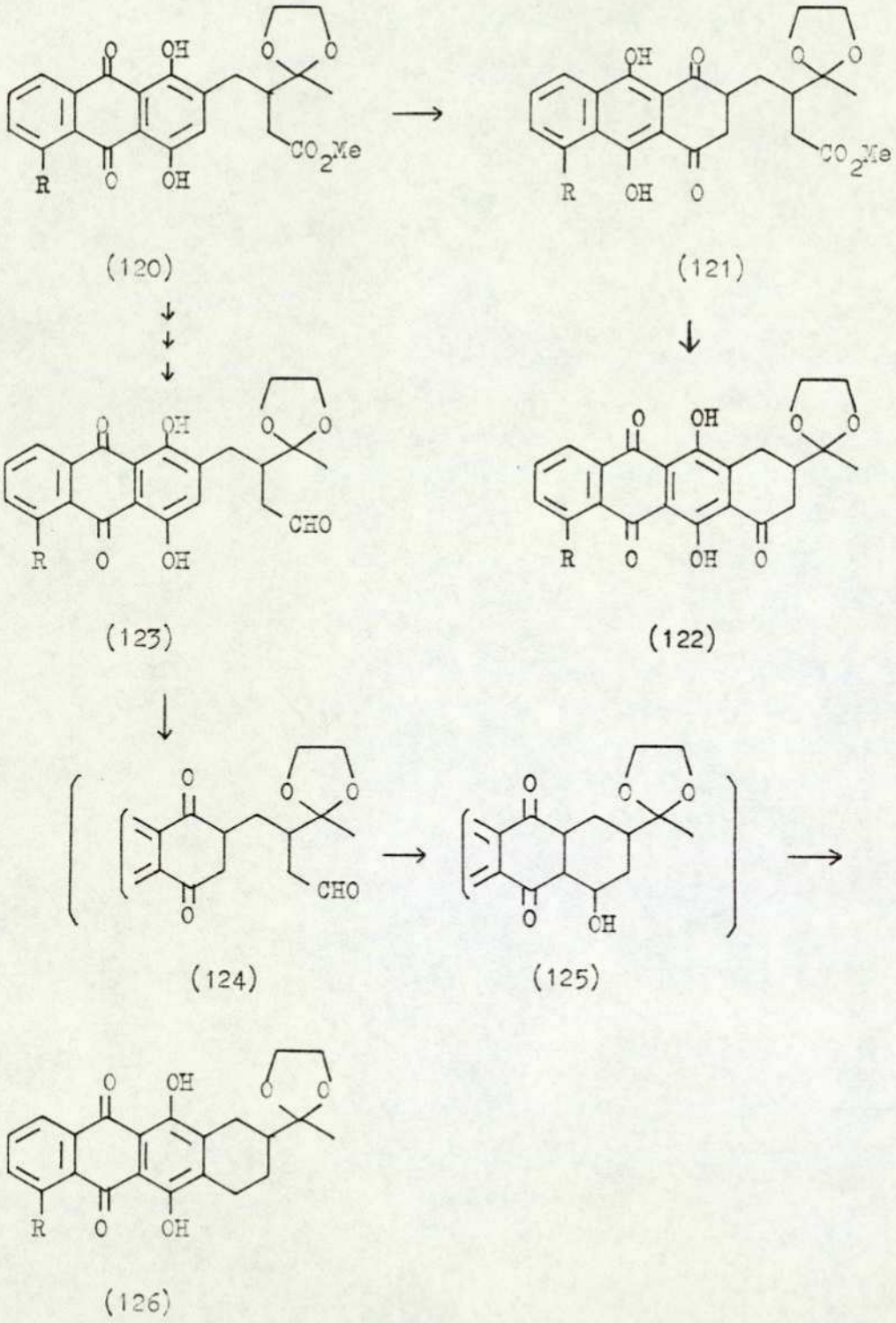
A possible route to the basic anthracyclinone skeleton containing the correct orientation of the substituents on rings A and D would involve the direct regiospecific cyclization of the anthraquinone (119).[38]



(119) R = H or Me

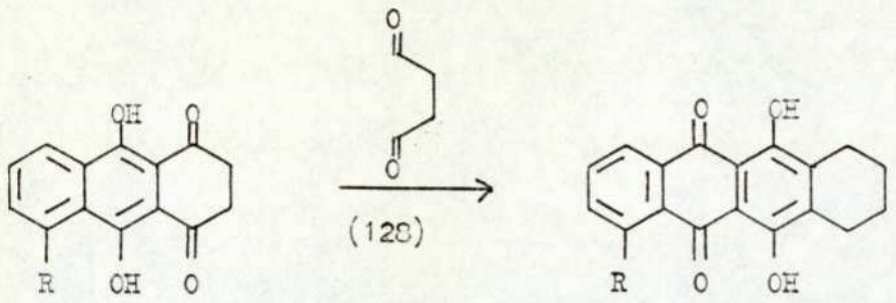
However, numerous attempts to catalyse the cyclization using conventional strong acidic or basic reagents were unsuccessful. The desired transformation was effected, however, by alteration of the electronic configuration of the anthraquinone ring system to a dihydro-anthraquinone derivative[38] (Scheme 11).

Thus, the anthraquinone (120a) was transformed into its leuco-form (121a), which, when treated with calcium oxide (as base) and zinc (as reducing agent to suppress back-oxidation) in ethylene glycol at 140° for 3 minutes, was cyclized to the tetracyclic system (122a) (50%). As the ester group in (121a) underwent exchange with the solvent, causing a lowering in yields, it was transformed into the aldehyde. Reduction and cyclization via the transient alcohol (125a) produced the ketal (126a) (> 50%).



Scheme 11 a) R = H b) R = OMe

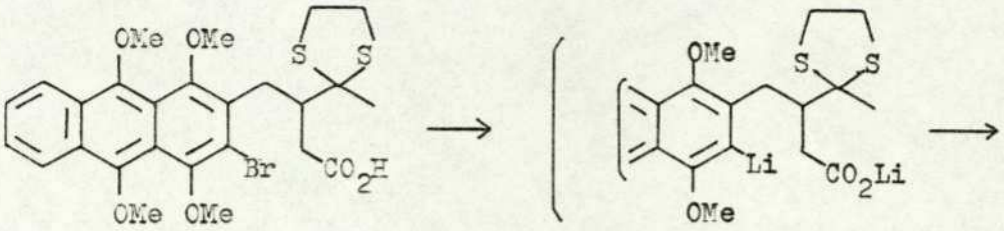
Attempts to cyclize the 4-methoxy derivative (121b) were unsuccessful and only traces of the ketone (122b) were isolated. Again, in order to increase the reactivity of the system, the ester (120b) was transformed into the aldehyde (123b), which, on treatment with basic dithionite afforded the tetracyclic system (126b) (52%). This intramolecular Marschalk[40] reaction proceeds *via* the intermediates (124b) and (125b) and Sih[39] reports that preliminary results on the isolation of the alcohol (125b) are encouraging.



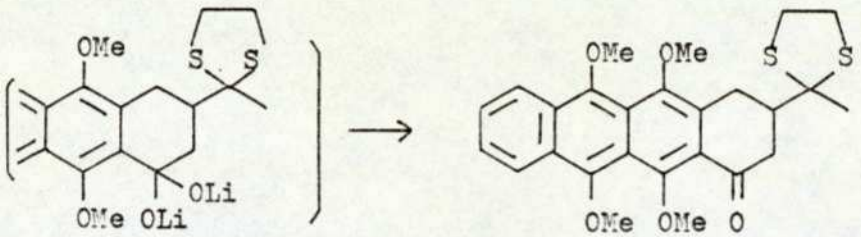
(127) R = H, OH, OMe (129) R = H, OH, Me

Scheme 12

A simple preparation of the basic tetracyclic ring system, also involving the Marschalk reaction, has been reported by Brown and Morris[41] (Scheme 12). They found that reaction of the leuco derivatives of 1,4-dihydroxyanthraquinones (127) with succindialdehyde (128) afforded the tetracyclic compounds (129) in good yields (60-80%). This sequence could provide a particularly flexible means of entry into this group of compounds and, as before, one feature yet to be exploited is the isolation of the intermediates containing a benzylic alcohol function.



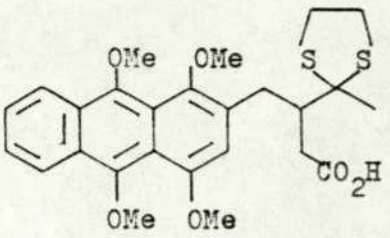
(130) (131)



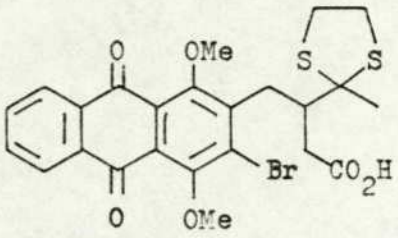
(132) (133)

Scheme 13

A recent preparation[42] of benzyocycloalkenones from o-bromophenyl-alkanoic acids has led to a regioselective entry into the aglycone system. Thus, treatment of the acid (130) (Scheme 13) with 2.5 equivalents of n-butyl lithium in tetrahydrofuran (THF) at temperatures ranging from -110° to 0°C afforded the ketone (133) in 55% yield. The reaction presumably proceeds *via* intermediates of type (131) and (132) and the by-products are usually the debrominated starting material (*eg.* (134)). Similar treatment of the methyl ester of (130) also affords the ketone (133).



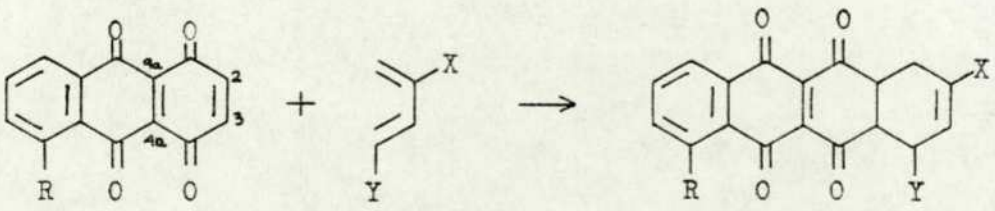
(134)



(135)

Interestingly the corresponding cyclization of the anthraquinone (135) failed, but the acid (134) was cyclised to the ketone (133) in near quantitative yield by trifluoroacetic anhydride at -40°. No details of this transformation were reported, but, in view of the work of Sih et.el[39], the development of this procedure could afford an attractive route to the aglycone system.

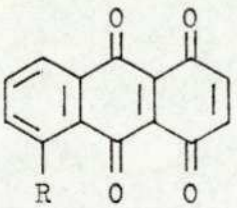
At a time when only Wong[23] had reported a synthesis of (±)-daunomycinone by a 22-step procedure, there was clearly a need for more direct and flexible approaches to the synthesis of the aglycones. One such approach, adopted by many chemists, was a Diels-Alder reaction of the type shown below:-



→ → → → Aglycones

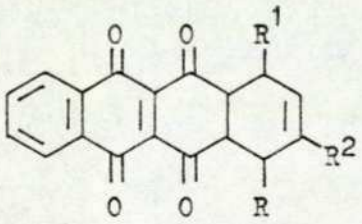
Whilst this route has certain synthetic advantages there are also two inherent difficulties. Firstly the initial Diels-Alder addition can occur at either the internal (4a, 9a) or external (2, 3) double bond and secondly, if linear annulation could be controlled, a problem of regioselectivity of addition is involved.

Initial studies by Inhoffen et.al[43] showed that the diquinone (136a) did indeed react as a bi-functional dienophile. Only with 1,4-diacetoxybutadiene was any end adduct (137) isolated; in other cases

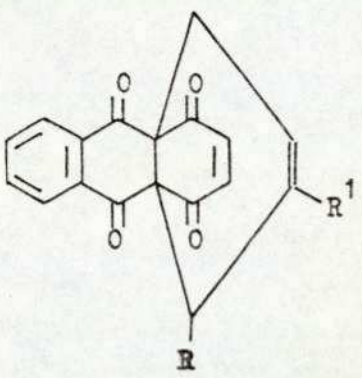


(136a) R = H

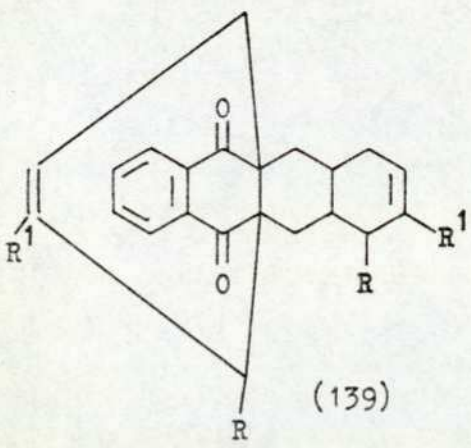
(136b) R = OH



(137) R = OAc, $R^1 = R^2 = H$



(138)

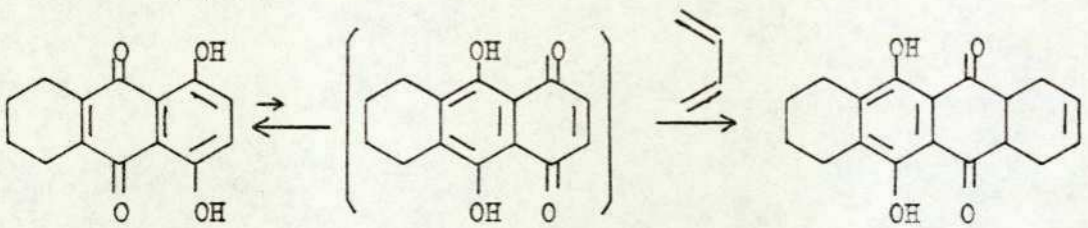


(139)

they found that the internal adduct (138) or diadduct (139) predominantly formed. Later work by Lee et.al[34] gave similar results. For example butadiene and 1-acetoxybutadiene gave mainly terminal adducts whereas 2-methoxybutadiene afforded the internal adduct.

Kelly et.al[44] also investigated the reaction of the diquinones (136a) and (136b) with a variety of diene systems. They again obtained similar results to previous workers and also observed that the diquinone (136b) gave a mixture of end adduct isomers. Having gained little success, their attention was drawn to an alternative approach[45] which involved removal of the internal addition mode.

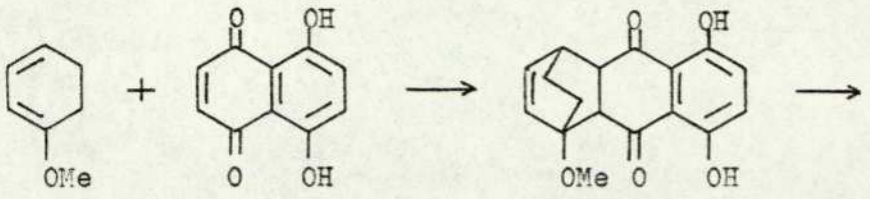
Farina et.al[46] had shown that an end adduct (142) could be obtained form the Diels-Alder reaction between the quinone (140) and butadiene (Scheme 14). The reaction proceeds via (141), the less stable tautomer of (140).



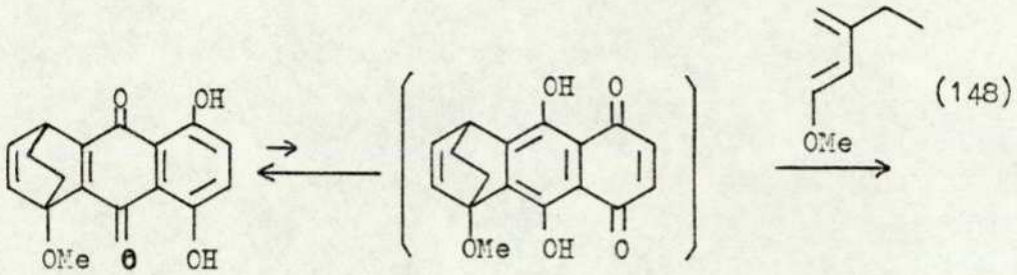
Scheme 14 (140) (141) (142)

Attempts to extend this to the fully aromatic derivative of (140) were unsuccessful. Thus, ring D had to be incorporated in a latent aromatic form. Kelly found the solution to this problem by an extension and amalgamation of previous work[46,47,48] and this is shown in Scheme 15.

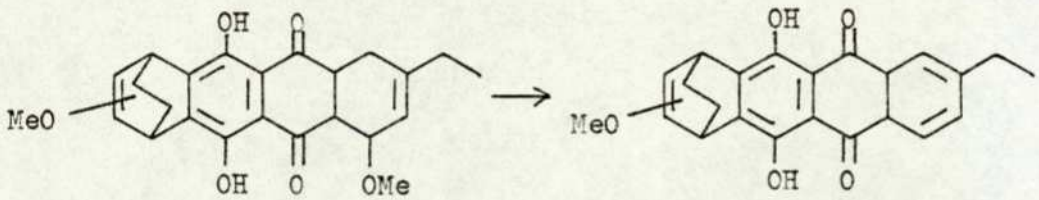
Reaction of the diene (143) with naphthazarin (144) gave the adduct (145) which underwent oxidation and tautomerization to (146). Reaction, via (147), with the butadiene (148) afforded tetracyclic system (149) (50% from (144)). In order to determine the position of the potential aromatic methoxyl group, (149) was oxidized to the aromatic derivative



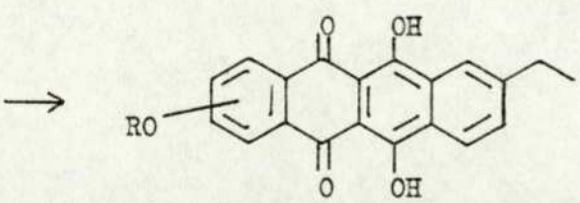
(143) (144) (145)



(146) (147) (148)



(149) (150)



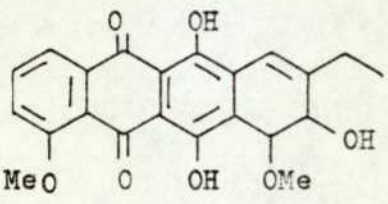
(151) R = Me

(152) R = H

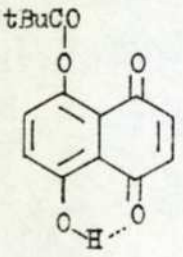
Scheme 15

(150), which when heated at 155° eliminates ethylene to give the naphthacenequinone (151). Comparison of demethylated compound (152) with authentic samples revealed that the major (80%) component was the isomer containing the hydroxyl group at C-1. The Diels-Alder reaction between (147) and (148) therefore proceeds in the regiochemically undesired sense.

Kelly et.al[49,50] have recently modified the procedure to obtain a regiospecific preparation of the tetracyclic system (153). The starting dienophile was the naphthazarin monopivalate (154) in which the conflicting influences of the peri-acyloxy and hydroxy groups operate in a complementary fashion and thus exert regiochemical control on the ensuing Diels-Alder reactions.



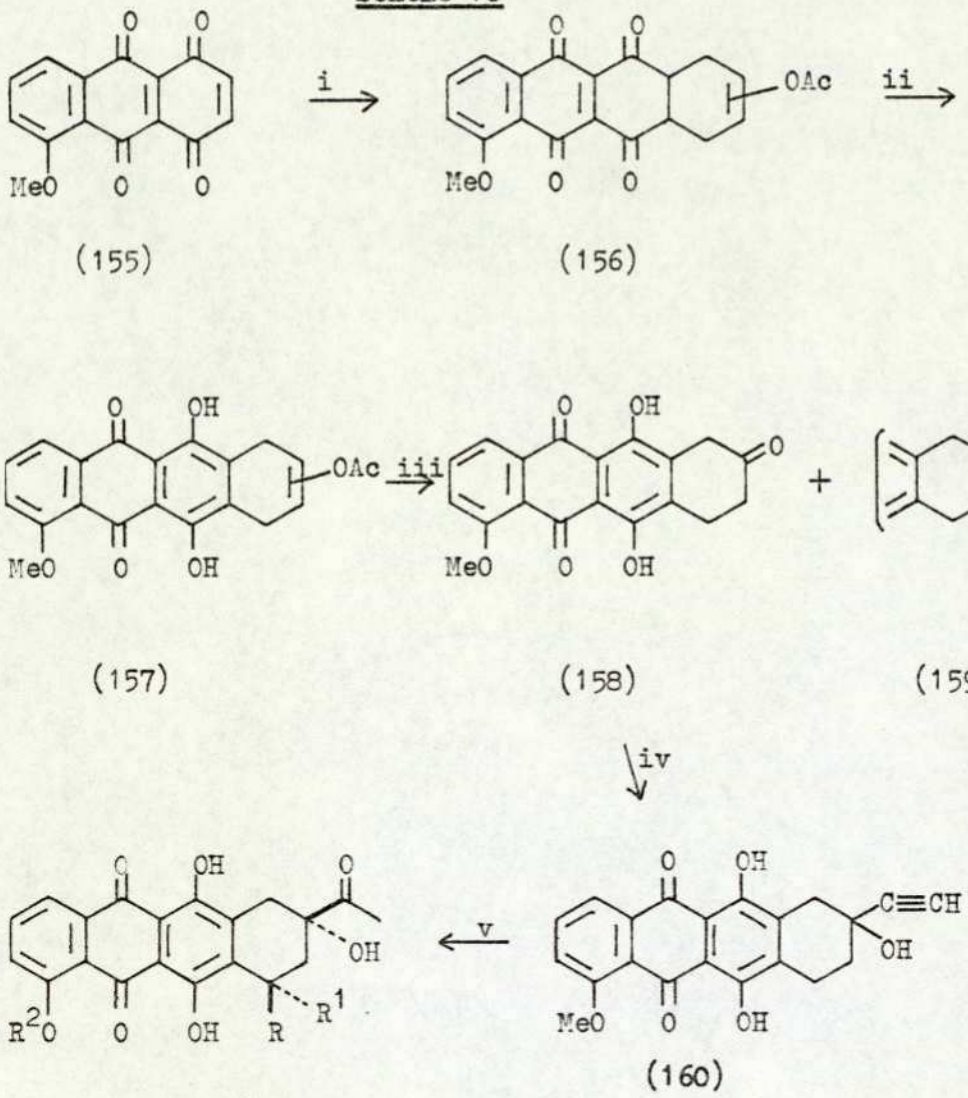
(153)



(154)

The successful application of the Diels-Alder reaction to the synthesis of aglycones has been reported by Kende et.al[32] (Scheme 16)

Scheme 16



(155) (156) (157) (158) (159) (160)

(161) R = R^1 = H, R^2 = Me

↓vi

(122) R = H, R^1 = OH, R^2 = Me —vii→ (24) R = R^2 = H, R^1 = OH

(162) R = OH, R^1 = H, R^2 = Me

Reagents: i, 2-acetoxybutadiene, AcOH, 25°, 4 days; ii, NaOAc AcOH, Δ; iii, EtOH, 6N HCl, Δ; iv, HC≡CMgBr, THF; v, Hg_2O, H_2SO_4/H_2O; vi,a) Br_2/CCl_4, b) H_2O/SiO_2; vii, $AlCl_3$, ØH.

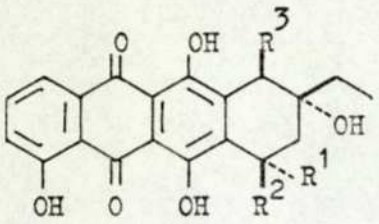
Their synthesis started from the highly reactive diquinone (155). By analogy with previously described work, it was concluded that internal addition to the diquinone (155) would be favoured by electron-rich dienes, and terminal addition by slightly electron-poor or unsubstituted dienes as was predicted by Hückel M.O. calculations. For example, 2-ethoxybutadiene would be expected to add to the internal double bond whereas 1,3-butadiene and, more importantly, 2-acetoxybutadiene would give mainly end adduct.

Thus, treatment of the diquinone (155) with three equivalents of 2-acetoxybutadiene gave 71% of a mixture of end adducts (156). These were converted to the corresponding anthraquinone tautomers (157) and thence to the ketones (158) and (159) by cleavage of the enol acetate function. Recrystallization gave a single isomer which was identified as (158) by comparison with a sample prepared by side-chain degradation of 7-deoxy-13-daunomycinol derived from natural daunorubicin[30]. Reaction of the ketone (158) with ethynyl magnesium bromide gave the ethynylcarbinol (160) which was hydrated to (±)-7-deoxydaunomycinone (161). This racemic material was identical in all chemical respects with an authentic sample obtained from hydrogenolysis of (±)-daunomycinone.

Racemic (161) was brominated using bromine in carbon tetrachloride under irradiation. In this manner, the product of free radical bromination at C-7 occurred whilst bromination of the enol position at C-14 was suppressed. Chromatography on moist silica gel plates hydrolysed the labile bromine and a 5:2:1 mixture of (±)-7-epidaunomycinone (162), (±)-daunomycinone (22) and starting material was obtained. Epimerisation

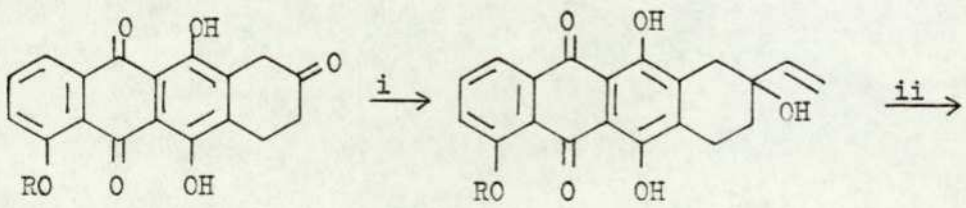
of (162) with trifluoracetic acid gave (±)-daunomycinone (22) in 76% yield (overall yield from (161), ca 50%). Conversion of synthetic (22) to (±)-carminomycinone (24) was achieved in nearly quantitative yield by O-demethylation with anhydrous aluminium chloride in benzene. A 3% yield of (±)- daunomycinone (22) was obtained from the diquinone (155) by the above seven step sequence.

The use of the ketones (155) and (163) as versatile intermediates has been elegantly demononstrated by Kende and Tsay[37] in their total synthesis of the rhodomycin aglycones (13), (15), (17) and (18) (Scheme 17).



	R^1	R^2	R^3	
(13)	H	OH	OH	α-rhodomycinone
(15)	OH	H	OH	β-rhodomycinone
(17)	H	H	OH	γ-rhodomycinone
(18)	H	H	H	10-deoxy- γ -rhodomycinone

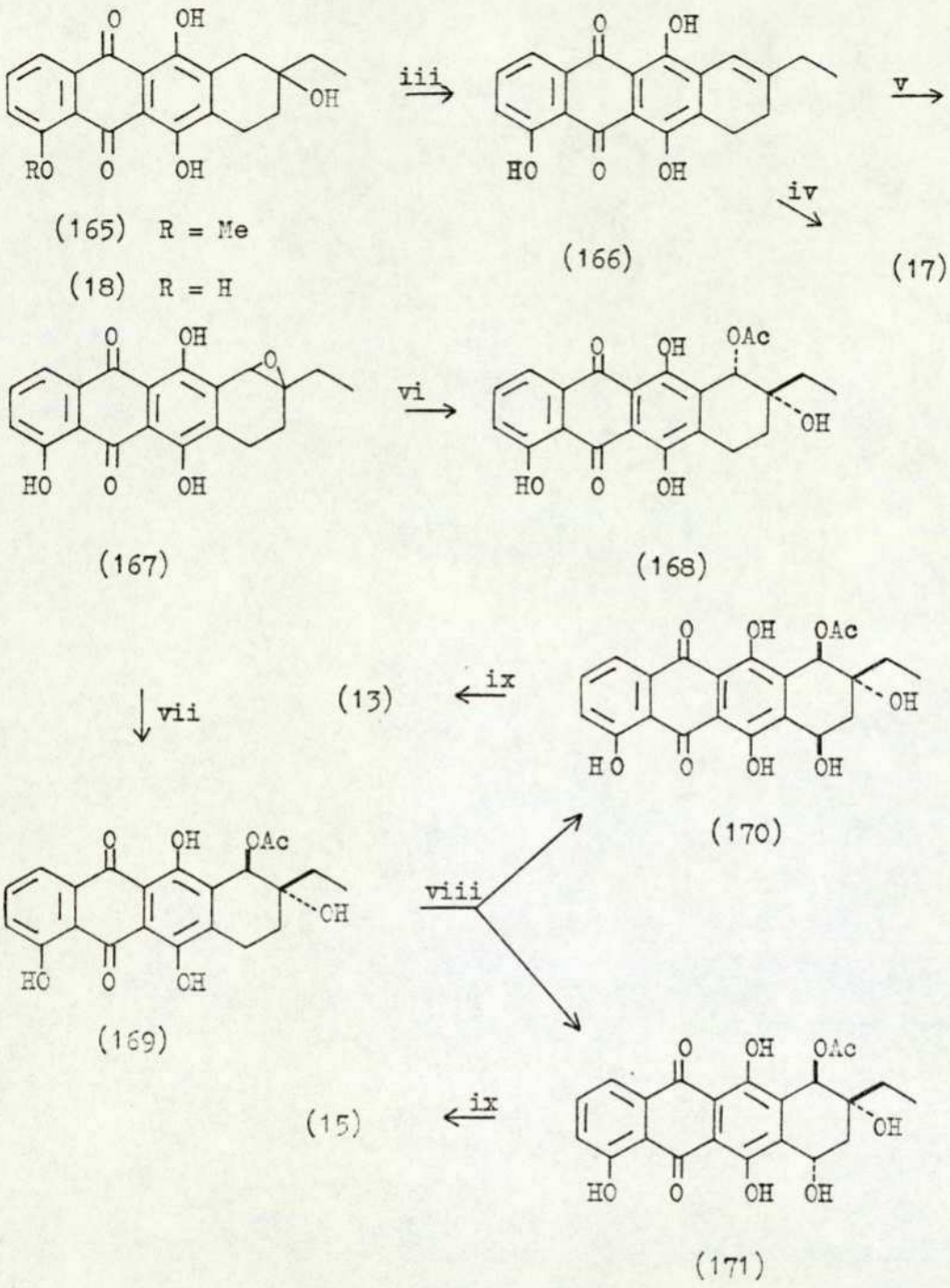
Scheme 17



(155) R = Me (164a) R = Me

(163) R = H (164b) R = H

(continued next page)



(165) R = Me

(18) R = H

(166)

(17)

(167)

(168)

(13)

(170)

(169)

(15)

(171)

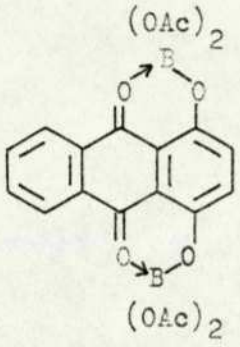
Reagents:- i, $CH_2{=}CH_2MgBr$, THF, -78°; ii, $KO_2CN_2CO_2K$, AcOH py; iii, $AlCl_3$, CH_2Cl_2; iv, o-sulphobenzoic anhydride, 30% H_2O_2, acetone; v, m-chloroperbenzoic acid; vi, AcOH; vii, AcOH-NaOAc; viii,a) Br_2, CCl_4, hυ, b) $AgOCOF_3$, Me_2SO; ix, 0.5N NaOH, EtOH

Reaction of the ketone (163) (obtained by demethylation of (155)) with vinyl magnesium bromide gave the vinyl carbinol (164a) (50%) which was reduced with diimide to (±)-10-deoxy-γ-rhodomycinone (18) (90%). In an analogous manner the alcohol (165) was obtained in 73% overall yield. It was then dehydrated and demethylated with aluminium chloride to the olefin (166), which was stereospecifically trans-hydroxylated to give (±)-γ-rhodomycinone (17). As attempts to introduce oxygen at C-7 by homolytic bromination of (17) led to oxidation at C-10, the olefin (166) was converted to the epoxide (167). With acetic acid, the epoxide (167) was selectively opened to give, predominantly, the cis-acetate (168). However, if a mixture of acetic acid and 2-4% sodium acetate was used then both (168) and the trans-acetate (169) were obtained in the ratio 1:9. Bromination of the acetate (169) gave the labile C-7 bromide which was treated with silver trifluoroacetate and then hydrolysed to give a 50% yield of a separable mixture of the alcohols (170) and (171) (1:1). Hydrolysis yielded the (±)-α- and (±)-β-rhodomycinones, (13) and (15), respectively.

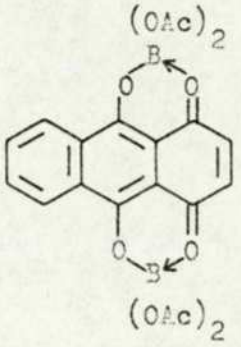
Two groups have investigated the reaction of systems that avoid the problem of addition at the possible "internal" and "external" ene centres of the diquinone (136a).

Mercer et.al[51] observed that the quinizarin diboroacetate is a hybrid with approximately equal contributions from both canonical forms (172a) and (172b). Thus, Diels-Alder addition occurs only at the 2,3-positions. However, problems of subsequent aromatisation have been encountered. For example, reaction with 1-methoxbutadiene gives benzoquinizarin (173) and, more importantly, 1-methoxy-3-trimethysiloxy-

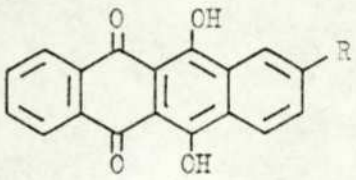
butadiene gives the 2-hydroxy derivative (174).



(172a)



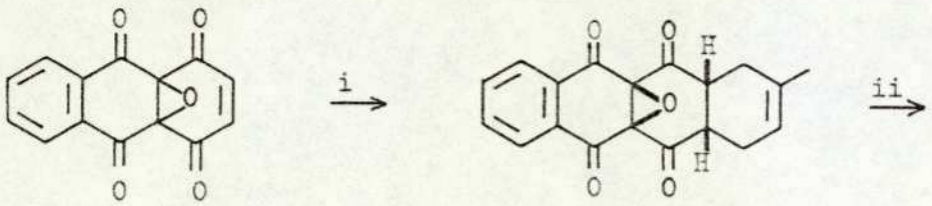
(172b)



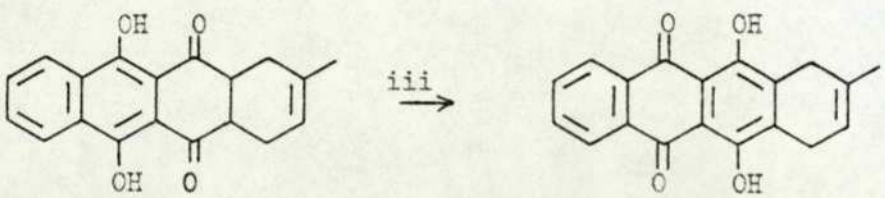
(173) R = H

(174) R = OH

Protection of the internal 4a,9a-double bond would extend the reactivity of the diquinone system. Stoodley[52] has reported that the epoxy-derivative (175), prepared in 50% yield from (136a) has the potential to fulfil this function.



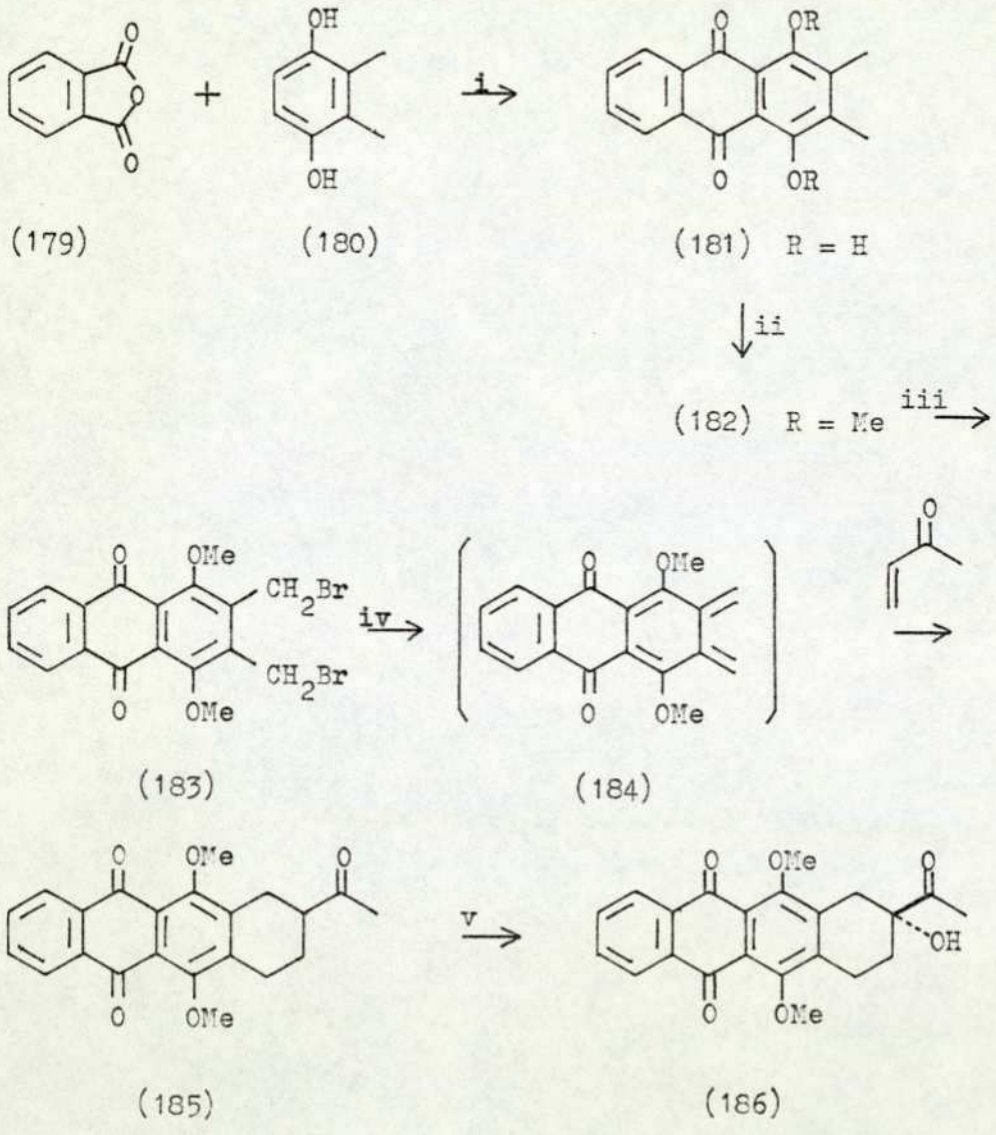
(175) (176)



(177) (178)

Scheme 18 Reagents: i, isoprene, benzene, $\triangle$; ii, sodium dithionite-methanol; iii,a) $Pb(OAc)_4$, AcOH, b), NEt_3,benzene, $\triangle$.

Reaction of the epoxide (175) (Scheme 18) with isoprene (a diene that reacts with the 4a,9a-double bond of (136a)[44]) afforded the adduct (176) in 90% yield. Attempts to directly deoxygenate the compound were unsuccessful. However, reaction with sodium dithionite-methanol afforded the dione (177) (35%) which was converted to the quinone (178) in 80% yield. The reaction of (175) with functionalized dienes would significantly extend the scope of the Diels-Alder route to anthracyclinones.



(179) (180) (181) R = H

(182) R = Me

(183) (184)

(185) (186)

Scheme 19 Reagents: i, $AlCl_3$, NaCl, 190°; ii, Me_2SO_4, K_2CO_3; iii, NBS, CCl_4, Δ ; iv, Zn, DMF; v,a) $KOBu^t$, DMF, O_2; b) $P(OEt)_3$.

An alternative Diels-Alder approach in which ring A is constructed from a dienophile rather than a diene has been reported by Cava and Kerdesky[53]. The sequence involves the Diels-Alder addition of a reactive o-quinodimethane intermediate (184) to the double bond of an α,β-unsaturated ketone (Scheme 19).

Phthalic anhydride (179) was condensed with 2,3-dimethylhydroquinone (180) and the product (181) methylated and brominated to give the key dibromide (183) in 73% overall yield. Reaction of the dibromide (183) with zinc dust in DMF in the presence of methyl vinyl ketone afforded the ketone (185) (52%), which was converted to the hydroxy ketone (186) in an overall yield from (180) of 21%. As the introduction of the hydroxyl moiety into C-7 has been reported by several groups,[23,36] the synthesis of (186) constitutes a new synthesis of 4-demethoxydaunomycinone (115). This efficient route should be flexible enough to allow the preparation of aglycone analogues.

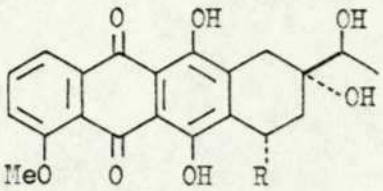
Microbial Transformations

Many of the anthracycline antibiotics exhibit antitumour activity and several members are considered to be effective clinical agents in the treatment of various cancers. However these compounds have also been found to be toxic. Microbial biomodification would be one way of preparing analogues which might exhibit the same activity whilst possessing diminished toxicity.

Depending on the strain of micro-organism used, certain anthracycline glycosides can be reduced to either the 7-deoxyaglycone, with or without side-chain reduction, or the anthracycline with just the side-chain reduced.

Wiley et.al[54] found that micro-aerophilically-grown Aeromonas hydrophilia, Citrobacter freundii and E. Coli, converted daunorubicin, nogalamycin, steffimycin, steffimycin B, steffimycinone and cinerubin A to the corresponding 7-deoxyaglycones. The transformation is formally a benzylic hydrogenolysis.

If, however, daunorubicin[55] was treated with a crude enzyme preparation of Streptomyces steffisburgensis, two products were obtained and identified as 7-deoxydaunomycinone (66%) and 7-deoxydaunomycinol (187) (31%). It was found that the conversion to 7-deoxydaunomycinone required NAD and that further reduction to (187) was catalysed by a NADP linked keto reductase.



(187) R = H

(188) R = daunosamine (40)

The microbial reduction of daunorubicin to daunorubicinol (188) has been observed by several groups[56,57], who found that the transformation could be carried out by various species. Similarly daunomycinone[58] and carminomycin[59] (24, R^5 = (40)). can be reduced only at the 13-carbonyl function to give the corresponding 13-hydroxy molecule.

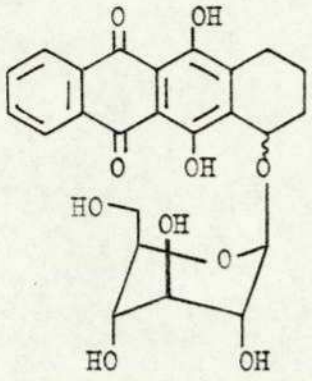
Semi-synthetic derivatives

The establishment of the effectiveness of adriamycin in the treatment of human malignancies has opened a new field in medicinal chemistry, and during recent years different important contributions to the chemistry of the anthracyclines have appeared in the literature. Not only has the synthesis of the tetracyclic ring system received consideration but also the synthesis of the glycosidic bond between the aglycone and the sugar.

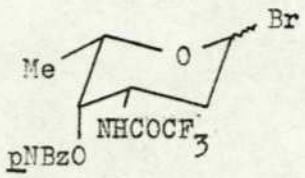
The main method used for the coupling of a suitably protected glycosyl halide to the aglycone is the Koenigs-Knorr reaction. As shown by several groups, the synthesis of glycosides using this reaction gives two diastereoisomeric compounds. For example Goodman et.al[11] found that the reaction of the tetracyclic alcohol (49) with acetobromoglucose in the presence of mercuric cyanide gave a good yield of the diastereoisomers (189), after removal of the protecting groups.

However, Acton et.al[60] have reported that the reaction of daunomycinone with the protected bromide (190) in the presence of mercury salts and molecular sieves, afforded only daunorubicin and none of the β-anomer.

There are two routes used to couple sugars to adriamycinone analogues. Either the coupling is performed with daunomycinone and then the deprotected product is converted to the adriamycin analogue by bromination at C—14 followed by hydrolysis,[61] or the hydroxymethyl ketone function is protected and then the coupling reaction is performed. An example of the latter comes from the work of Arcamone et.al[62]. Treatment of adriamycinone with 2,2-dimethoxypropane under anhydrous acid conditions afforded the dioxolane (191). Coupling of (191) with the chloride (192)



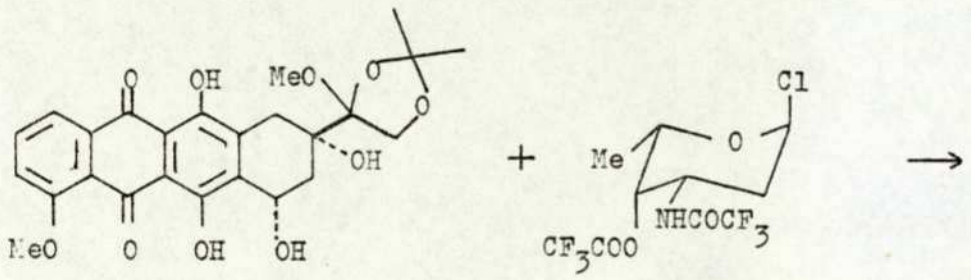
(189)



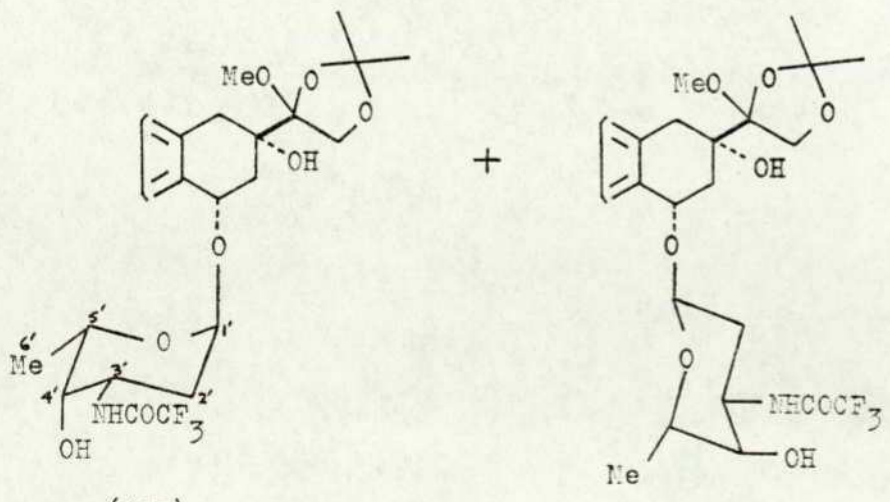
(190)

pNBZ = P-nitrobenzoyl

(Scheme 20) under standard conditions afforded the two anomeric glycosides (193) and (194) which, on deprotection, gave adriamycin and its β-anomer, respectively. The α and β-anomers in this series can be easily identified from their p.m.r. spectra[63,62].



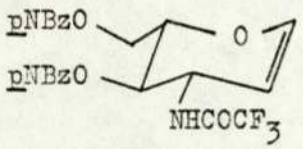
(191) (192)



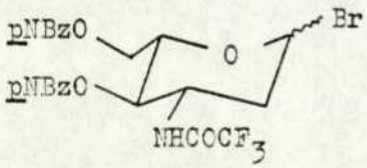
(193) (194)

Scheme 20

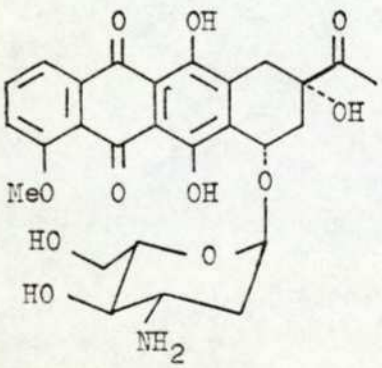
A coupling procedure which does not lead to anomeric mixtures has recently been reported[64]. The key intermediate for the stereocontrolled glycosidation of daunomycinone was the protected olefinic sugar (195). When (195) was reacted with daunomycinone in benzene containing a catalytic amount of toluene-p-sulphonic acid, the only compound obtained, after deprotection, was 4'-epi-6'-hydroxydaunorubicin (196) in 56% yield. When the preparation was repeated using the bromide (197) in the presence of mercury salts and molecular sieves, the final products were the α-anomer (196) (15%) and also the corresponding β-anomer (6%).



(195)

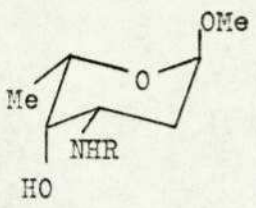


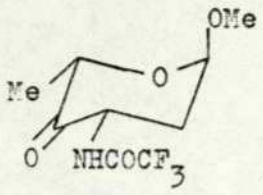
(197)

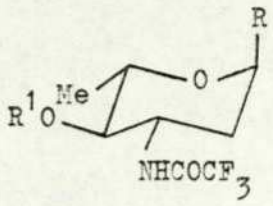


(196)

So far the sugar conformations have been those found in "natural" sugars. However, as will be seen in the next section, epimerization at the 4'-position will have an effect on the biological activity of the systems.







(194) R = H

(195) R = $COCF_3$

(196)

(197) R = OMe, R^1 = H

(198) R = OH R^1 = H

(199) R = R^1 = $COCF_3$

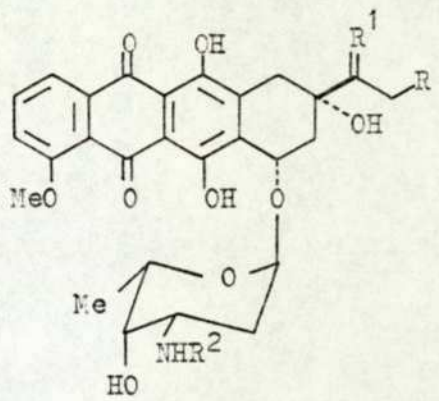
(200) R = Cl, R^1 = $COCF_3$

Conversion[62] of methyl-L-daunosamine (194) to the N-trifluoroacetyl derivative (195) followed by oxidation with ruthenium tetroxide gives the keto-sugar (196). Reduction with sodium borohydride results in stereoselective formation of the equatorial alcohol (197) which can be converted through to the protected sugar (200). Condensation with daunomycinone affords 4'-epidaunorubicin and the corresponding β-anomer. (194) has also been converted to 4-deoxydaunosamine[65].

Other aminosugars have been prepared starting from natural sugars,[67,68] and 4-deoxy-4,l,-daunosamine[69] and d,l-triacetyldaunosamine[70] have been obtained by total synthesis using a stereospecific non-carbohydrate approach.

2-Deoxy sugar glycosides of ε-rhodomycinone (20) have been synthesized but these compounds show only marginal activity[71].

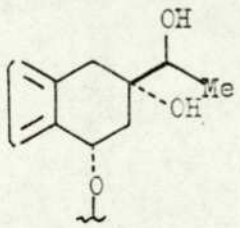
Another obvious approach to the development of new antitumour agents lies in the chemical modification of the very active compounds, daunorubicin and adriamycin, and derivatives of the side-chain ketone[72,73,74,75], N-acetyl derivatives of the amino group[72,74,76] and esters of adriamycin at the C-14 hydroxyl group[77] have been prepared. Examples of some of the types of compounds prepared are given below:-



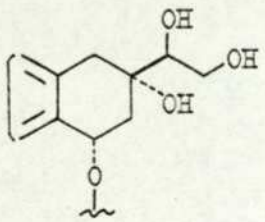
(201)	R	R^1	R^2	
a	H	NOH	H	
b	H	$NNHCONH_2$	H	
c	H	$NNHCOCH_2OH$	H	
d	H	$NNHCOC_6H_5$	H	Rubidazone
e	H	$NNHCOC_6H_4X$	H	
f	H	O	COMe	
g	H	O	$COCH_2NMe_2$	
h	H	O	CSNHPh	
i	OCOMe	O	H	
j	$OCOCH_2Ph$	O	H	
k	O-CO- 	O	H	

The "adriamycin esters (201 i-k)" were prepared by treating 14-bromodaunorubicin with the sodium or potassium salt of the appropriate organic acid.

Reduction of daunorubicin and adriamycin by potassium borohydride affords the alcohols (188) and (202), respectively[78]. These alcohols have

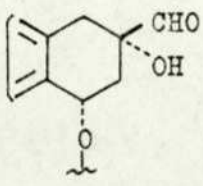


(188)

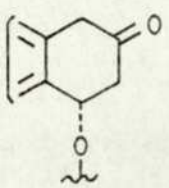


(202)

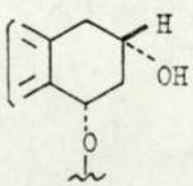
been used to prepare [14-C^{14}] -[79] and 9-deacetyldaunorubicin.[30] Selective[79] periodate oxidation of the C-13 diol in (202) afforded the aldehyde (203), which, on treatment with C^{14}-diazomethane, gave C-14 labelled daunorubicin. Periodate[30] oxidation of (188), followed by reduction of the ensuing ketone (204) afforded 9-deacetyldaunorubicin (205) and, the C-9 epimer (206). These compounds have been used to investigate the stereochemical requirements in the anthracycline antibiotics, Smith et.al[30] have



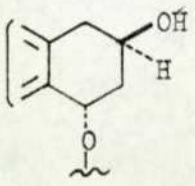
(203)



(204)



(205)

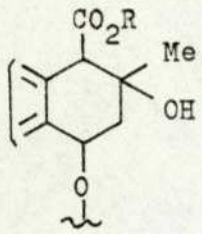


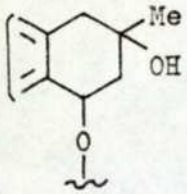
(206)

reported the degradation of daunorubicin to the non-asymmetric ketone (158)

and the refunctionalization of ring A to adriamycin. Possible methods of side-chain elaboration have also been evaluated using the β-tetralone system as a model[31].

Because of the rather modest antitumour activity and undesirable side-effects, nogalamycin (38) never became a clinically useful agent. The parent compound[81] has been hydrolysed to nogalamycinic acid (207) which could then be decarboxylated to nogamycin (208). The activity of these derivatives is reported to be superior to (38) and at least the equal of adriamycin.





(38) R = Me

(207) R= H

(208)

Biological Aspects

A brief review of the biochemistry of the anthracyclines, previously described, is given but as studies on pharmacology, toxicology, therapeutic applications, and general medical significance of these drugs have been the subject of several recent conferences and reviews,[20,82,83,84,85,86,87,88.] they will not be discussed.

It is generally believed that the main target for the biological action of the anthracyclines is DNA.[21,86,87,89,90,91,92] It is proposed that the anthracyclines bind by an intercalative process in which the aromatic chromophore is intercalated between partially unwound base-pairs, and the sugar is hydrogen-bonded to the nucleic acid backbone through its amino group.

Thus structure-activity relationships are of considerable importance for the establishment of structural requirements for action and, therefore, contribute to the understanding of the mechanism of action of the drugs. The results of the biological activity of the new glycosides show that analogues modified in the stereochemistry at C-4' and/or C-1' are still bioactive; the semi-synthetic analogues display non-identical ratios of effective doses in different tests, thus suggesting the possibility of different selectivity of action; and also that 4'- epiadriamycin possesses the same degree of activity as adriamycin but a lower cytotoxic activity in cultured cells[62,93]

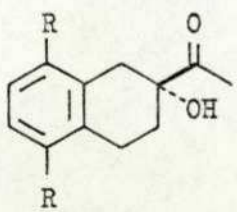
Recent reports[94] have shown that the interpretation of the daunorubicin - DNA model will lead to more active derivatives of these drugs. It was proposed that removal of the bulky 4-methoxy group on

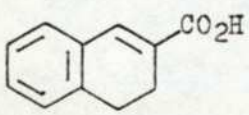
ring D would give a molecule that could intercalate more effectively. DiMarco et.al[95] have studied several 4-demethoxydaunorubicin derivatives and found that they did indeed bind better to DNA than daunorubicin and that they were effective in treatment of cancer at much lower dose levels[96]. They also came to the conclusion that stereochemical inversion at positions 7 and 9 markedly decreased the DNA-binding and that this inversion was more critical than inversion of configuration at position 1 in the amino-sugar.[95] For example, 9-deacetyl daunorubicin (205) is more active than the corresponding C-9 epimer (206)[80]. 4-Demethoxydaunorubicin is as effective as daunorubicin at doses 4 to 8 times lower. The β-anomer of 4-demethoxydaunorubicin was active at doses 8 to 13 times higher than those of its corresponding α-anomer, and 4-demethoxy-7,9-diepidaunorubicin and its β-anomer were devoid of any biological activity at the doses tested.[96]

Conclusion

Adriamycin has continued to show dramatic clinical efficacy along with serious toxicity. In spite of the drawbacks, its success against solid tumours has led to a great deal of research centred around the anthracycline nucleus.

Many notable advances have been made. 4-Demethoxydaunorubicin[96] was the first totally synthetic compound to exhibit a decrease in toxicity and an increase in activity compared to daunorubicin and adriamycin[97]. The 4-demethoxy compound was prepared from S(-)-1,4-dimethoxy-6-hydroxy-6-acetyltetralin (209) using a modification of the procedure reported by Wong et.al[23]. Model studies in the asymmetric synthesis of the ring A system have been reported[98]. Tarashima et.al[98] have developed a highly efficient asymmetric bromolactonization reaction which produced the optically active hydroxy-ketone (210) from the α,β-unsaturated acid (211) in more than 90% optical yield.





(209) R = OMe

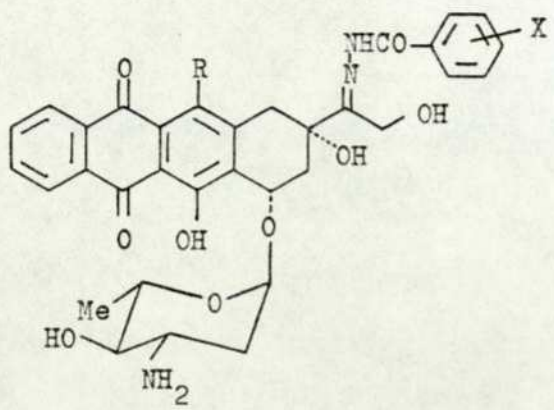
(210) R = H

(211)

Rubidazone (201d) (daunorubicin benzhydrazone) has a decreased cardiotoxicity relative to adriamycin and this compound[75] has been used as a base for a quantitative structure-activity relationship. The low toxicity and excellent activity of the analogues (201e) are most encouraging.

Recent screening has resulted in a large number of aklavinone- and pyrromycinone-based glycosides with potent activity[99,100,101]. These results, together with the increased activity found in the 10-decarbomethoxy derivative of nogalamycin should lead to the reinvestigation of the other anthracyclines. The way is now open to prepare more active analogues of these compounds either <u>via</u> the more flexible synthetic routes,[29,32,33,36,42,53] or by using the semi-synthetic methods already known.

It is interesting to speculate as to how long it will be before a derivative of the type (212) is prepared and tested:-



(212)

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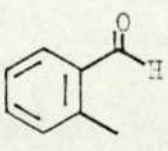
Results and Discussion

Dienolate Anion/Benzyne Interactions

Introduction

The initial aim of the research described in this thesis was to examine the preparation and reaction of dienolate anions and similar species. The work represents a radical extension of earlier work on the related, neutral, dienol derivatives.[1,2,3] In this earlier work the synthetic potential of the process known as photoenolisation was explored. Photoenolisation is the molecular rearrangement, induced by irradiation with u.v. or visible light, of certain α,β-unsaturated ketones, aldehydes and, in particular, aromatic carbonyl compounds bearing an o-alkyl substituent. For example, when o-tolualdehyde (213) is irradiated with u.v. light, it rearranges to the dienol (214). The photoenol (214) is a short lived species which readily undergoes either thermal reversion to the starting ketone or, if the irradiation is carried out in the presence of a dienophile, such as dimethyl acetylenedicarboxylate, a Diels-Alder addition can occur producing an adduct e.g. the dihydronaphthalene (215)[1].

Such cycloadditions were applied to the synthesis of some members of



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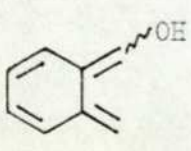
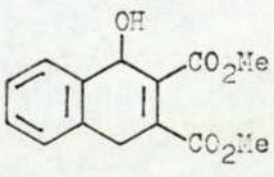
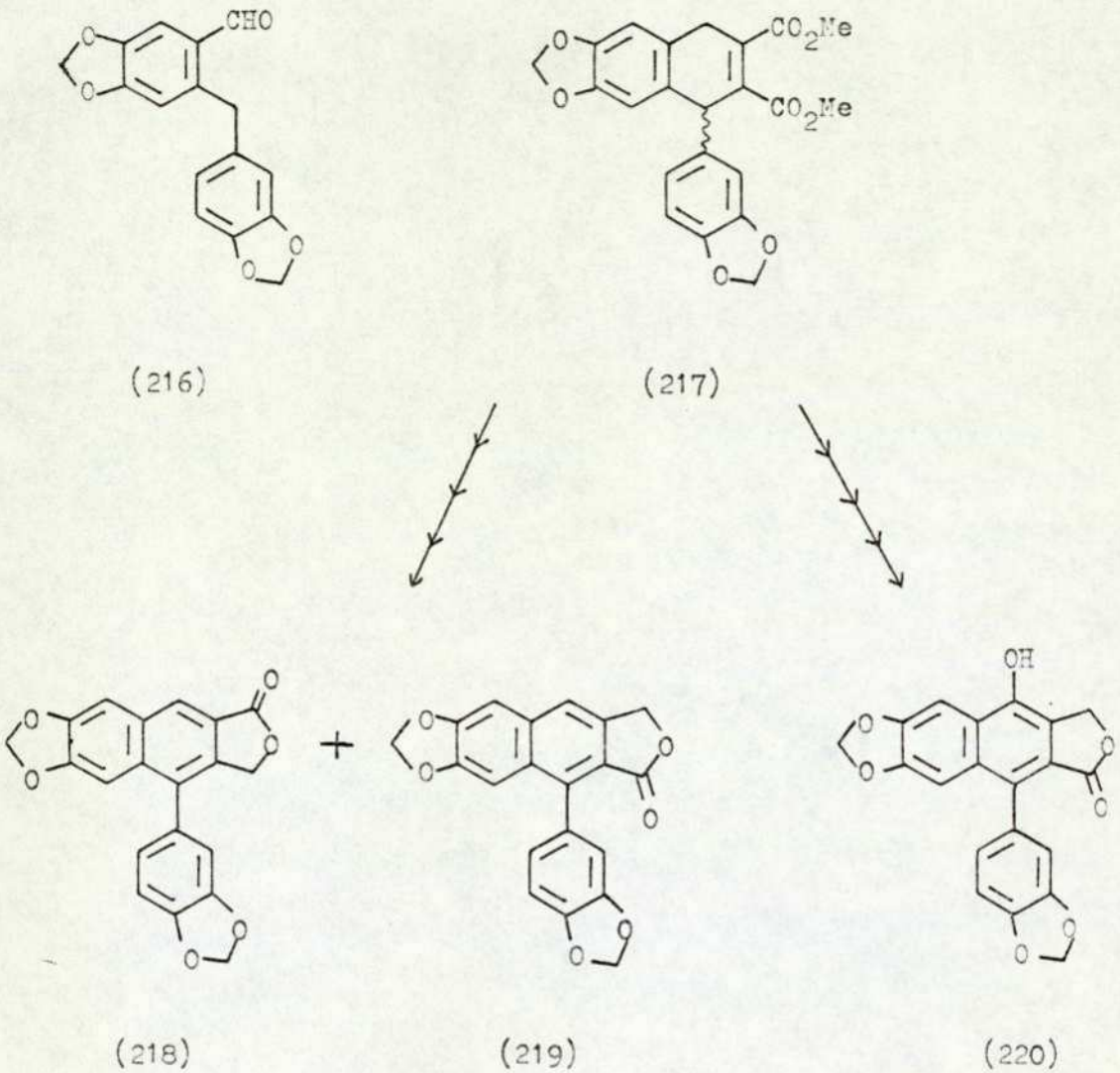


(214)



(215)

the lignan family.[4] The synthetic sequence involved the photochemically induced cycloaddition of an aryl aldehyde (216) to dimethyl acetylenedicarboxylate, affording the dihydronaphthols (217), which were subsequently transformed to the lignans justicidin E (218), taiwanin C (219) and taiwanin E (220) (Scheme 21).



(216) (217)

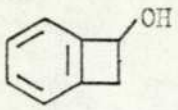
(218) (219) (220)

Scheme 21

Similar studies with 2-alkyl-3-acylchromonones afforded a new photochemical route to benzoxanthenones.[3,5]

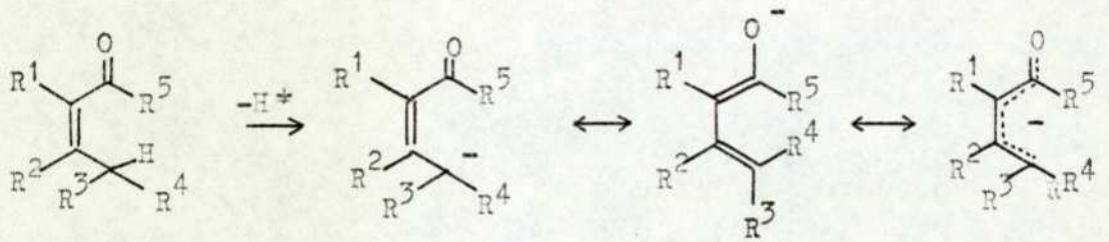
An alternative to the photoenolisation process was subsequently discovered in the thermal ring-opening reaction of benzocyclobutenols, which produces the same reactive intermediates. For example, the

parent compound (221) was found to undergo facile ring-opening to produce the dienol(214), which could either revert to the corresponding photoenol precursor (213), or participate in Diels-Alder cycloaddition reactions.[2,6]



(221)

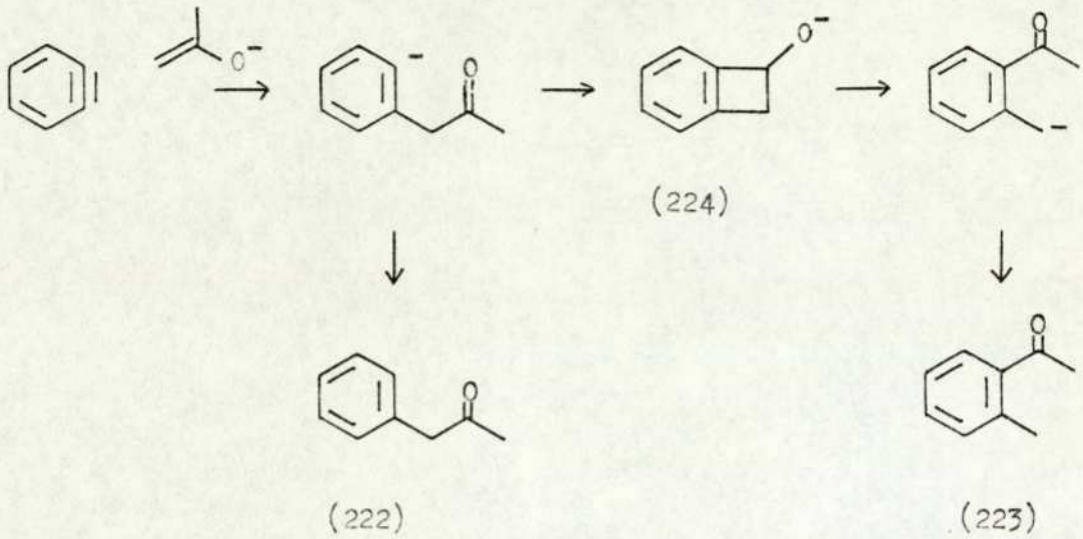
A completely different approach to the use of dienols in synthesis was the base-induced removal of a γ-proton from an α,β-unsaturated ketone. This produces the related species, a dienolate anion (Scheme 22).



Scheme 22

A brief study of these reactive species by Wallace[3] started with the need to prepare substituted benzocyclobutenols. Caubère et.al[7,8] had shown that benzocyclobutenols can be generated from the reaction of ketone enolate anions with arynes. Under the reaction conditions used, however, the benzocyclo-compounds are not stable and undergo ring-opening to the corresponding aromatic ketones. For example, the enolate anion of acetone reacts with bromobenzene and sodamide to afford inter alia the ketones (222) and (223) (Scheme 23). The latter is presumably obtained via the

benzocyclobutenolate anion (224).[7] In certain circumstances, benzocyclo-

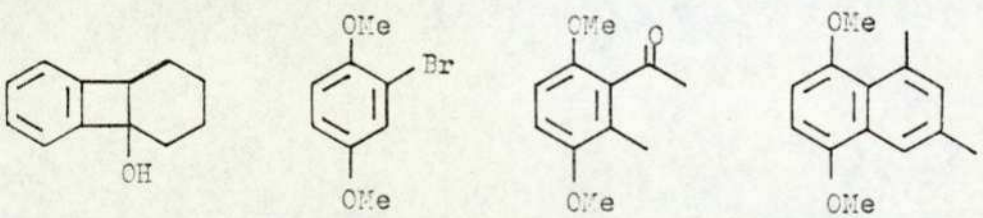


(224)

(222) (223)

Scheme 23

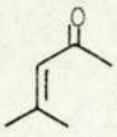
butenol derivatives have been isolated, for example, the alcohol (225), derived from the cyclohexanone enolate anion, bromobenzene and sodamide in tetrahydrofuran (THF)[8].



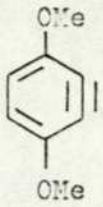
(225) (226) (227) (228)

In an attempt to extend the sequence to the preparation of substituted benzocyclobutenols, Wallace repeated[3] the reaction of acetone enolate anion with the alternative benzyne precursor (226). The major product was the ketone (227), but a very interesting by-product of the reaction was the naphthalene (228). The formation of (228) was most

readily attributed to the reaction of mesityl oxide (229), from the base-induced self-condensation of acetone, with the benzyne (230). When the reaction was repeated with mesityl oxide (229) in place of acetone, a



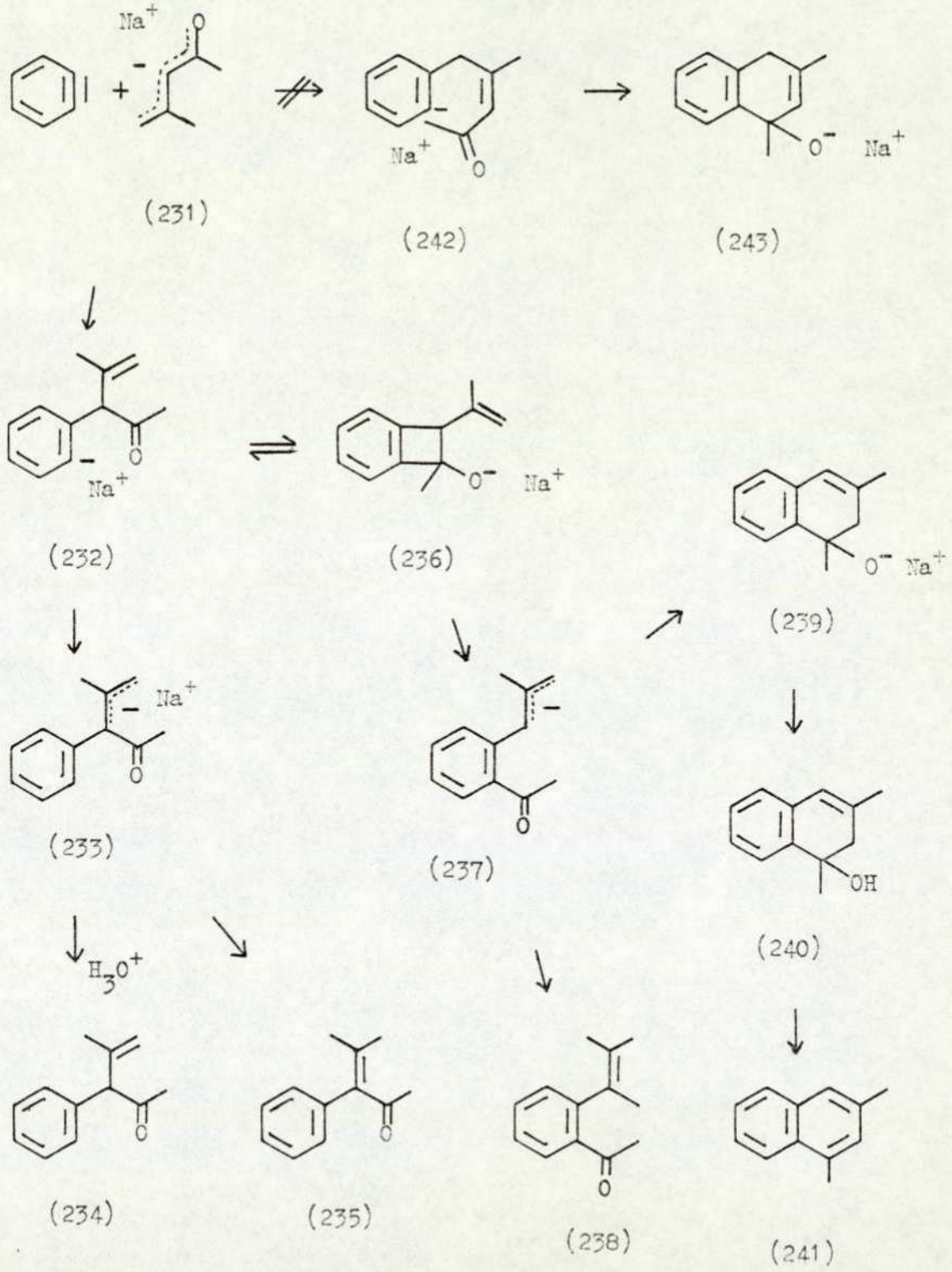
(229)



(230)

34% yield, based on (226), of the naphthalene (228) was obtained. The reaction was then applied to other substituted benzyne precursors and α,β-unsaturated ketones and esters. The mixed base system of lithium diisopropylamide/sodamide/sodium t-butoxide was used in this work which provides a general route to substituted naphthols and naphthalenes.[9]

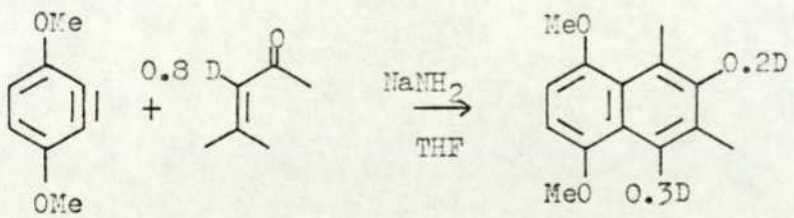
Caubère et.al.[10] examined all the products of the reaction and found the ketones (234), (235) and (238), as well as the naphthalene (241); (Scheme 24) summarises Caubère's results.



Scheme 24 [10]

Caubère proposed that the mechanism involved the initial attack of the anion (231) on the benzyne *via* the central α-carbon-atom. The resulting carbanion (232) can then undergo several processes. Intramolecular protonation affords (233) which on work-up gives the ketones (234) and (235). Alternatively rearrangement gives the benzocyclobutenolate anion (236) (c.f. Scheme 23), which undergoes ring-opening to (24); protonation leads to (238) or further rearrangement gives (239) and thence the naphthalene (241).

The process leading to (242) was described by Caubère as "less probable". Simple M.O. calculations indicate that the maximum negative charge resides on the central α-carbon atom[11a] and this has been demonstrated by alkylation reactions[16]. It is, however, possible that steric and conformational effects brought about by the reaction medium and metal ion could promote reaction *via* the γ-position.[11b] In order to determine the reaction pathway, Wallace repeated the reaction with deuterated mesityl oxide (244). (Scheme 25).



(230) (244) (245)

Scheme 25

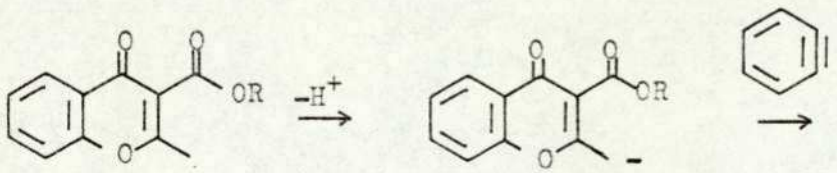
From Caubère's mechanism (Scheme 24), attack of the central α-anion of (244) on the benzyne species would result in a label at C-8 of the naphthalene (245); alternatively the γ-anion would give C-6 deuteration. The observed isotopic distribution indicated that both mechanisms were operative but, because of some loss of deuterium label during the experiment, it was not possible to determine the preferred pathway.

The labelling experiment had, however, shown that the reaction of dienolate anions and benzynes to give cyclic compounds can occur. It was the primary aim of this work to extend the synthetic use of the reaction to cyclic anion precursors, thus suppressing α- and enhancing γ-anion attack.

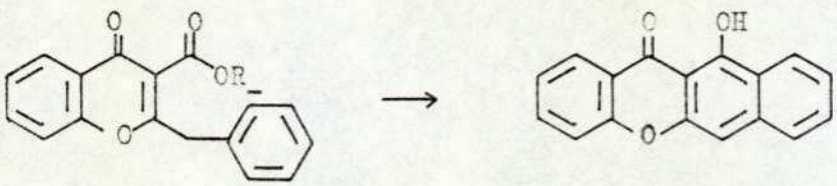
Intermolecular Cyclizations

Benzoxanthenone Synthesis

The first cyclic anion precursor examined was the chromone system (246), and a simple benzoxanthenone synthesis was envisaged (Scheme 26). It was felt that the keto-ester system would enhance the acidity of the methyl protons, stabilize the resulting anion (247) and that the ester group would facilitate ring closure to the benzoxanthenone (248).



(246) (247)

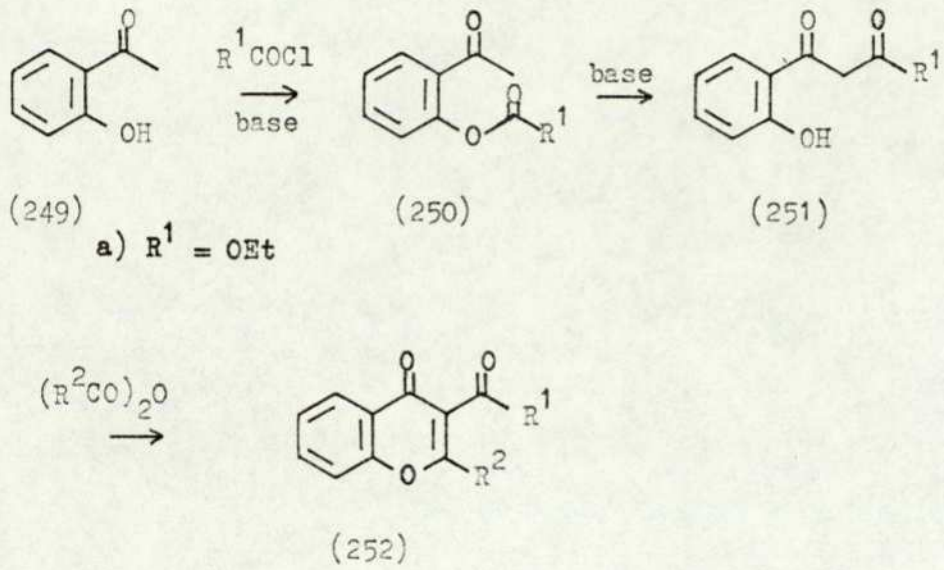


(248)

Scheme 26 a) R = Et

2-Alkyl-3-acylchromones (252) are readily available through a general procedure starting from commercially available 2-hydroxyacetophenone (249) (Scheme 27).

The route to the final product (252) depends on the availabilities of the acid chloride, R^1COCl, and the anhydride, $(R^2CO)_2O$. Previously no 3-carboxychromones had been prepared and an attempt was made to

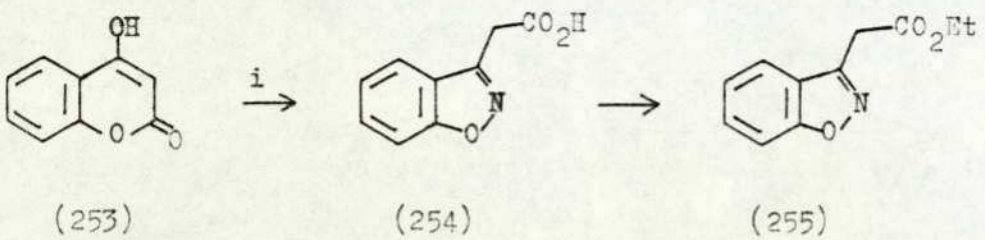


(249) a) R^1 = OEt (250) (251)

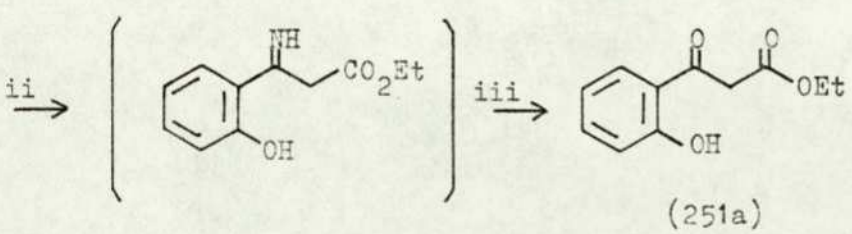
(252)

Scheme 27

extend the 3—acylchromone synthesis (Scheme 27) to the preparation of the carboxyethyl derivative (246a). Treatment of (249) with ethyl chloroformate in the presence of pyridine gave the carbonate (250a), however attempts at the base-catalysed rearrangement to the β-keto ester (251a) were unsuccessful.



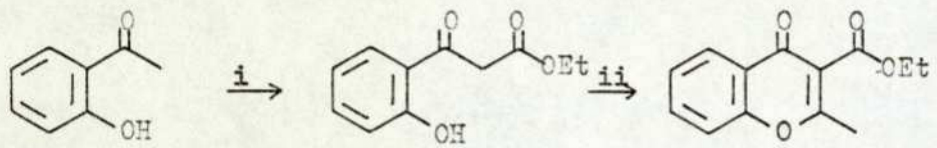
(253) (254) (255)



(251a)

Scheme 28 Reagents: i, NH_2OH; ii, H_2/Pd, EtOH; iii, AcOH.

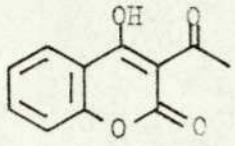
Compound (251a) had previously been prepared by Casini and co-workers[12] from 4-hydroxycoumarin (253) (Scheme 28). On treatment with hydroxylamine, (253) gave 1,2-benzisoxazole-3-acetic acid (254) which was esterified to the ethyl ester (255). Hydrogenation, followed by acid treatment of the unstable product, gave the β-ketoester (251a). Attempts by the Italians to distil the β-ketoester (251a) resulted in formation of the starting compound (253), as did treatment of (251a) with 2N sodium hydroxide solution. As an alternative route a single, one-step preparation of (251a) was examined (Scheme 29).



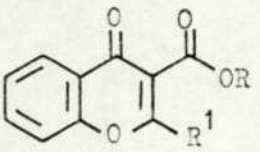
(249) (251a) (246a)

Scheme 29 Reagents: i, NaH, $(EtO)_2CO$, Et_2O; ii, NaOAc, $(MeCO)_2O$.

Slow addition of 2-hydroxyacetophenone (249) to a mixture of sodium hydride and diethyl carbonate in refluxing ether gave, after acid work-up and careful distillation at reduced pressure, the β-ketoester (251a) in 78% yield. Treatment of (251a) with acetic anhydride under the standard conditions gave a good yield of 3-ethoxycarbonyl-2-methylchromone (246a), m.p. 67-9°, of consistent analytical and spectral data. If the reaction mixture was heated too long or water was not excluded then 3-acetyl-4-hydroxycoumarin (256) was the only product.



(256)



(257a) R = Et, R^1 = H

(257b) R = R^1 = Me

At this time a literature report appeared on the preparation of the 3-carboxy chromones (257a,b) and their reaction with acids and bases.[13] The chromones (257) were prepared *via* the standard methods from (251a) (prepared in turn by the method of Casine *et.al.*[12]) and similar facile base-induced rearrangements to the respective 3-acyl-4-hydroxycoumarins were found. These observations may well explain the scarcity of 3-carboxychromones in the literature, since in those preparations of chromones, vigorous basic conditions are required. In view of these limitations, the sequence shown in (Scheme 29) should provide an easy and convenient route to these compounds.

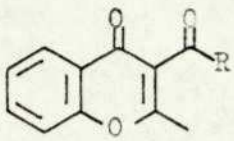
Having obtained the chromone (246a) in good yield, the proposed route to benzoxanthenones was examined (Scheme 26). In his naphthalene synthesis Wallace[3] had developed a mixed base system of lithium di-isopropylamide (LDA)/sodamide/sodium t-butoxide. The tetrahydrofuran-soluble lithium amide base was used only to generate stable dienolate anions, as it proved inferior to sodamide in benzyne formation. The

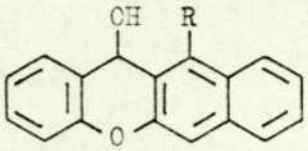
general procedure involved addition of the α,β-unsaturated carbonyl system to a solution of LDA in THF at -10°. After one or two hours, sodamide and sodium t-butoxide were added and the mixture cooled to -70°. The benzyne precursor was then added and the reaction mixture slowly warmed to room temperature (16 hours).

When this procedure was repeated with the chromone (246a) and bromobenzene, none of the expected benzoxanthenone (248) was formed. The reaction afforded a mixture (t.l.c. analysis), the major component being a brown, polar material which gave an indistinct p.m.r. spectrum. The only identifiable material obtained from these tars was a small amount of the starting chromone (246a). Following this failure, the stability of (246a) to several bases was examined. LDA and sodium hydride were found to be very destructive. Sodamide, however, appeared to be more suitable; the reaction with (246a) affording less polar material. Having investigated the base system, the question of benzyne precursor was re-examined. 2,5-Dimethoxybromobenzene (226) was chosen as the benzyne precursor, since any products resulting from anion addition to the benzyne should contain the methoxy groups and would thus possess a distinctive n.m.r. spectrum. In the event, reaction of (246a) and (226) with sodamide in THF resulted in no benzoxanthenone formation. The majority of material was again of a polar nature. Small amounts of the starting materials were recovered, but in all the fractions examined by p.m.r. spectroscopy, no material containing methoxy groups was observed.

As a result of the instability of the 3-carboxychromone (246a), attention was turned to the 3-acyl derivatives (258a,b). Both compounds were available *via* the standard route (Scheme 27). Treatment of 3-acetyl-

chromone (258a) with sodamide and bromobenzene produced a similar reaction mixture to that from the 3-carboxy derivative; the majority of material





(258a) R = Me

(258b) R = Ph

(259a) R = Me

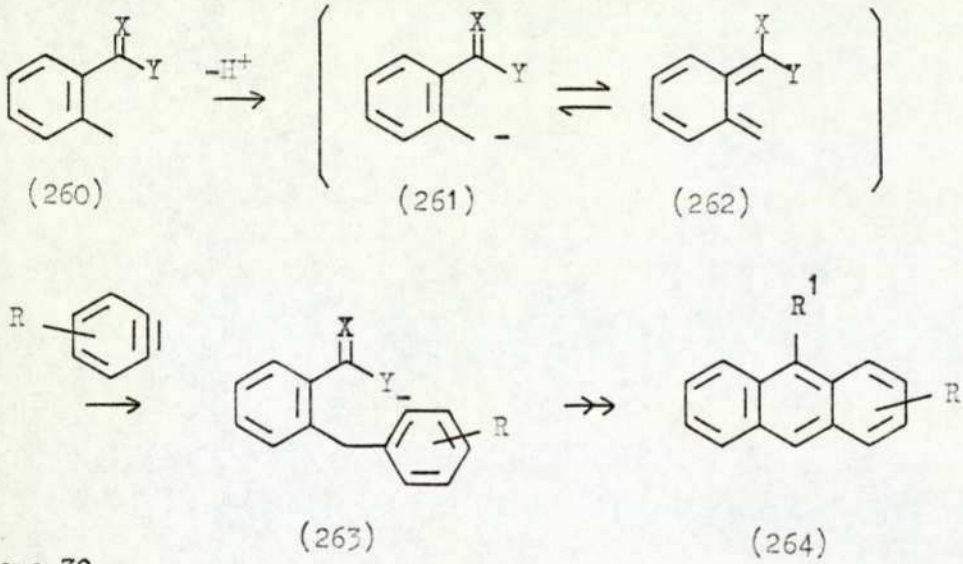
(259b) R = Ph

being very polar and none of the expected benzoxanthenone (259a) being formed. With the phenyl system (259b), a small amount of two fluorescent non-polar bands were obtained after preparative chromatography of the reaction mixture. The expected product, the benzoxanthenone (259b), is a known compound[14] with ultra-violet spectral characteristics; λ_{max} inter alia 311 n.m. (log ε 3.81), 323 (3.86)and 390 (3.63). None of these absorptions were observed in the u.v. spectrum of the two non-polar bands.

The main difficulty in these systems appears to be the instability of the carbanion and when this instability is considered with the long reaction times needed to generate the benzyne, it is not surprising that no cyclized material was obtained from these reactions.

Anthracene Synthesis

As an alternative to the chromone nucleus, the dienolate anion synthon was incorporated into the aromatic nucleus (260) and a route to substituted anthracenes was devised (Scheme 30). Suitable electron-withdrawing substituents ortho to the methyl group would, it was argued, enhance both the formation of the anion and its stability. Reaction with benzyne followed by ring closure would afford an anthracene (264).

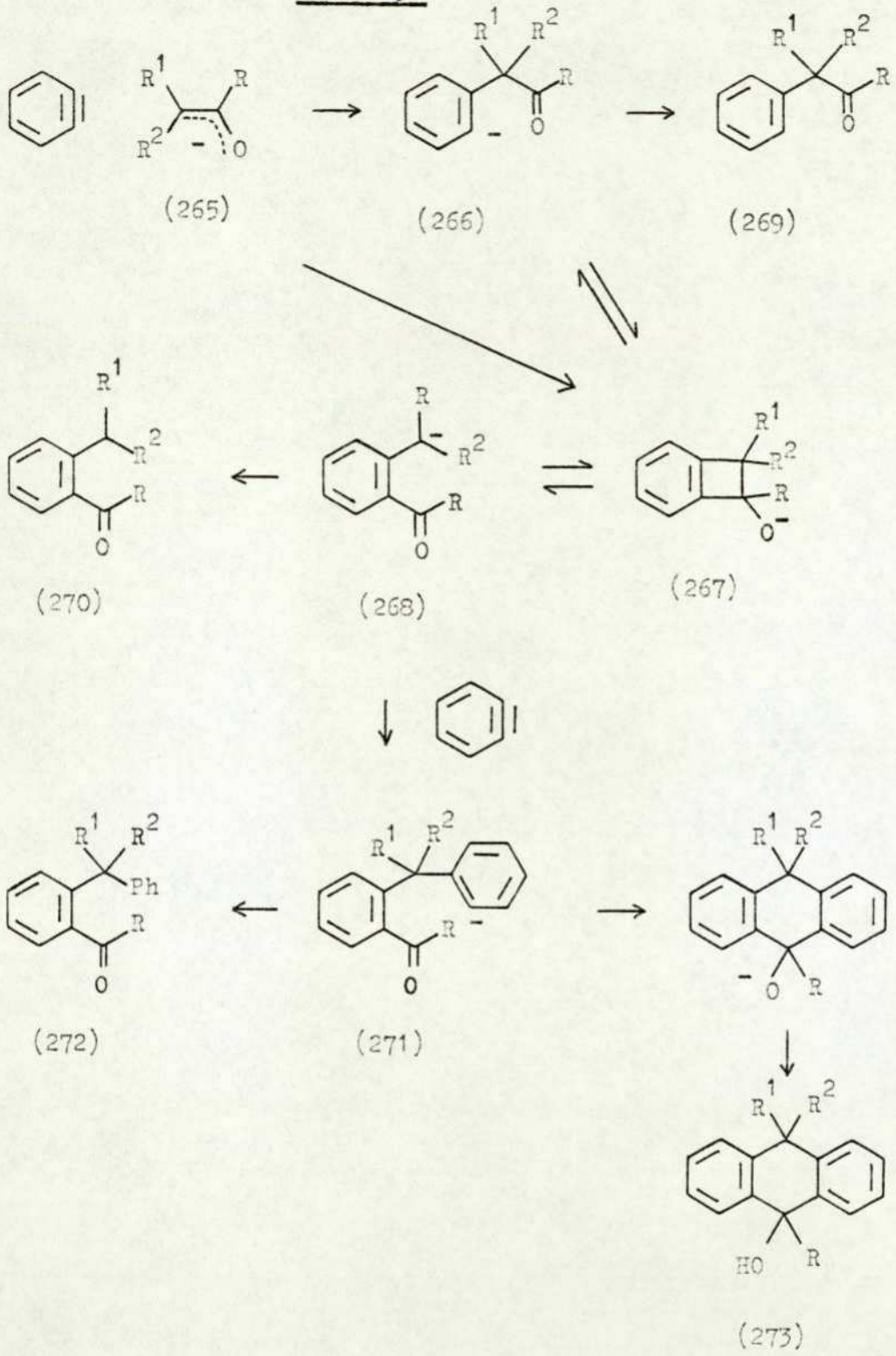


(260) (261) (262) (263) (264)

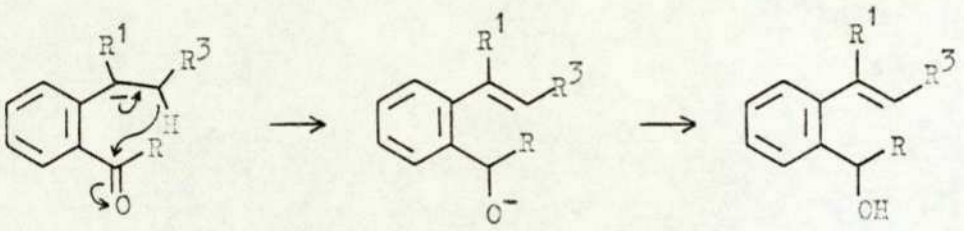
Scheme 30

The literature revealed that a sequence similar to Scheme 30 had been proposed by Caubère and his coworkers in their papers[15,16,17,18,19] concerning the reactions of ketone enolates (265) with sodamide and halobenzenes in THF. Whilst the products obtained in aprotic media depend on the experimental conditions and the ketone, all the compounds obtained could be explained in terms of the intermediacy of the anions (266), (267) and (268). Their work with cyclic[8,20,21,22] ketone enolate condensations and on ring opening of alcohols derived from (267) (eg (225)) led them to consider the general mechanism, shown in Scheme 31, where

Scheme 31[17]



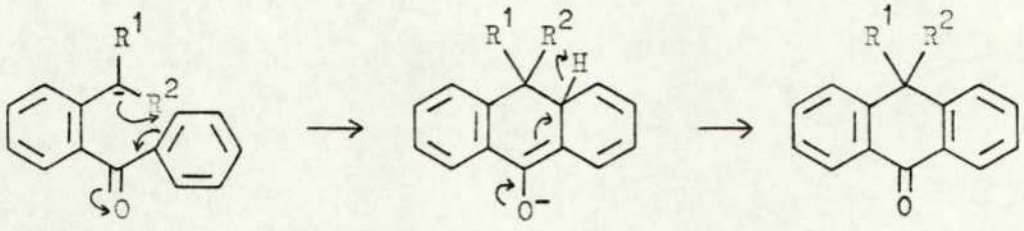
(265) condenses with benzyne to yield (266) and/or (267) and (266), (267) and (268) are equilibrated. Although with the acyclic ketones, the alcohols corresponding to the anions (267) were never obtained. If the ketone had $\underline{\alpha}$ and $\underline{\alpha}'$ methylene groups (eg. diethyl ketone)[17] only compounds of type (269) and (270) were isolated, but when there were at least two substituents $\underline{\alpha}$ and $\underline{\alpha}'$ (eg. t-butyl isopropyl ketone), no products of type (269) were formed and only compounds derived from the anion (268) were obtained, i.e. (270), (272), (273) and, when $R^2=CH_2R^3$, the alcohol (274) (Scheme 32).



(268) (274)

Scheme 32[19]

With aryl aliphatic ketones, the only products isolated were (274), (276) and in some cases (273). The amount of cyclic compound obtained was found to be dependent on the reaction temperature. In the case of isopropyl phenyl ketone[18], at -5° only traces of (276) were obtained and (273) (38%) was the major component. However, at 45° the anthrone (276) (28%)was the major product. The formation of (276) is shown in Scheme 33 and will be discussed later (page 114).

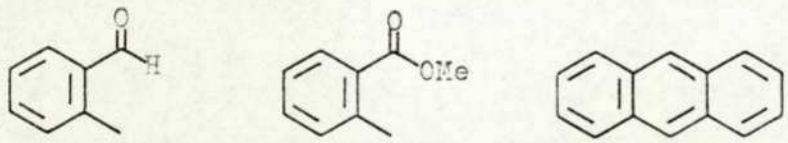


(268) (275) (276)

Scheme 33

With the proposed intermediacy of the anion (268), its reaction with benzyne to give (271) and cyclization to compound (273), Caubère's proposed mechanism appeared to give support to the route to anthracenes shown in Scheme 30.

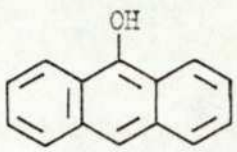
Several compounds of the required structure (260) were available and the system was initially examined with o-tolualdehyde (213) and methyl o-toluate (277).



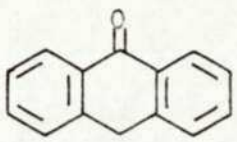
(213) (277) (278)

Treatment of the aldehyde (213) with LDA in THF produced an orange solution, to which was added sodamide/sodium t-butoxide, followed by bromobenzene. Acid work-up afforded a brown gum from which was isolated an impure sample of anthracene (278) (ca 1%), identified from its U.V.

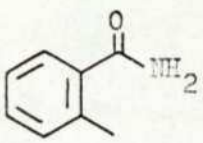
spectrum and t.l.c. properties by comparison with authentic material. The use of hexamethylphosphoramide (HMPA) as co-solvent did little to enhance the reaction as the yield of (278) was increased to only ca 4%. The ester (277) proved to be even less successful. Neither of the expected products, anthrol (279) or the tautomeric anthrone (280), were observed, but from the polar coloured reaction mixture was isolated 2-methylbenzamide (281). The ester grouping was thus demonstrated to be too labile with respect to the benzyne base.



(279)

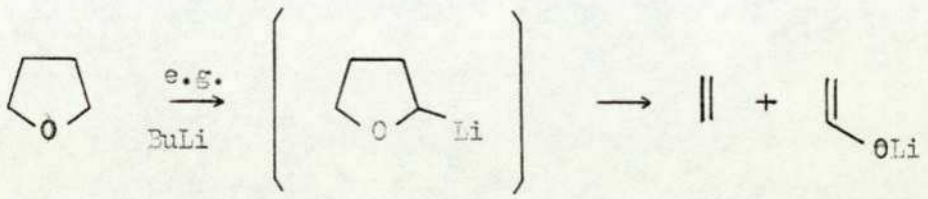


(280)



(281)

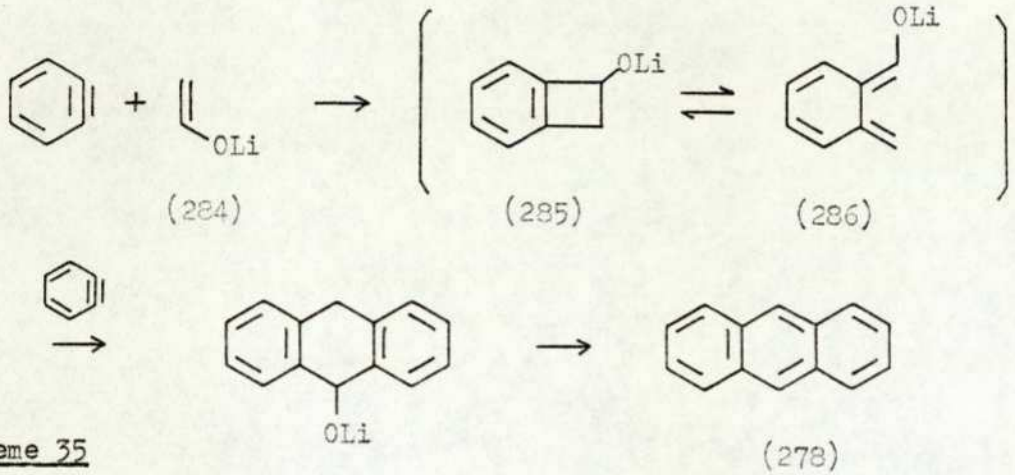
At this time there appeared in the literature a report by Fleming[23] of a simple 'one-pot' synthesis of symmetrical 9,10-unsubstituted anthracenes from a sequence involving benzynes and the enolate anion of acetaldehyde (284). Tetrahydrofuran is known[24] to react with strong bases to give the anion (282) which decomposes to ethylene (283) and the enolate (284) (Scheme 34).



(282) (283) (284)

Scheme 34

The reaction of the enolate anion (284) with benzyne gives the benzocyclobutenol anion (285) (cf., Caubère et al.[17] Scheme 31), but this, Fleming proposed, would decompose to give the o-quinone dimethide (286), which would be trapped by benzyne to give anthracene (278)(Scheme 35).

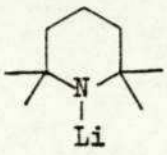


Scheme 35

Olofson[25] has reported that the strong, proton-specific base N-lithio-2,2,66,-tetramethylpiperidine (LiTMP) (287) reacts with aryl halides to form benzynes, and Fleming successfully used this base system for both anion and benzyne generation. In this manner bromobenzene was added to an excess of LiTMP in refluxing THF, and the major neutral product was anthracene (278) in 63% yield. Similarly, p-bromoanisole (288) gave, as a 1:1 mixture, 2,6-(289) and 2,7-dimethoxyanthracene (290) (66%).

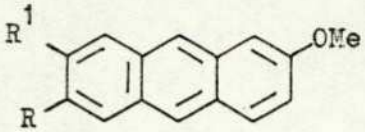
Fleming carefully verified that the reaction pathway followed that shown in Scheme 35. When the reaction was carried out at a low temperature no anthracene was formed. No other solvents (such as glyme) afforded anthracene as one of the products. If the butyl lithium and tetramethylpiperidine were mixed at reflux temperature and then the reaction mixture was cooled to 0°, before addition of bromobenzene, then a 40%

yield of anthracene was obtained.



(287)

(288)



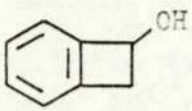
(289) R = OMe, R^1 = H

(290) R = H, R^1 = OMe

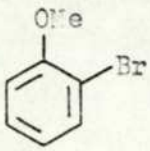
In view of Fleming's[23] results, the previous low temperature reaction between o-tolualdehyde (213) and bromobenzene was repeated with LiTMP (287) as the base for both anion and benzyne formation, but again no anthracene (278) was formed. In an attempt to achieve the elevated reaction temperatures used by Fleming, the reaction was repeated in refluxing benzene, but this gave only traces of anthracene. The use of HMPA as co-solvent did little to increase the yield. Attempts to confirm anion formation by alkylation with methyliodide were also unsuccessful; none of the expected 2-ethylbenzaldehyde or any compounds derived from it were obtained and no starting aldehyde (213) was recovered.

In view of the difficulties encountered with o-tolualdehyde (213), attention was turned to the use of benzocyclobutenol (221) as a dienolate anion synthon. It has been reported[26] that on treatment with aqueous sodium hydroxide benzocyclobutenol (221) is smoothly converted to o-tolualdehyde

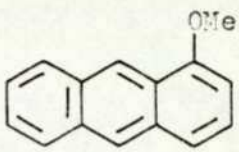
(213). Also, both Caubère[17] and Fleming[23], in their reaction schemes, propose that the intermediate benzocyclobutenolate anions undergo ring-opening to give reactive species of the type (261)/(262) which then react with benzynes to afford cyclic compounds. Accordingly benzocyclobutenol (221) was reacted with amide base and the trapping of any reactive species with benzyne was examined.



(221)



(291)



(292)

In Fleming's reaction sequence (Scheme 35) the reactive intermediates derived from the benzocyclobutenolate anion (285) are formed in the presence of benzyne (as they have been generated from benzyne) and consequently are quickly trapped to afford a high yield of anthracene. In an attempt to emulate these conditions the effect of the ratio of (221) : (291), the addition rate and the temperature on the reaction of benzyocyclobutenol (221) and o-bromoanisole (291) with LiTMP in THF was examined. The results are shown in Table 1.

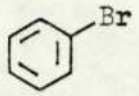
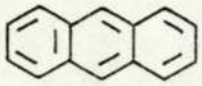
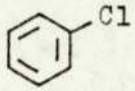
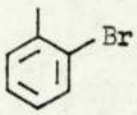
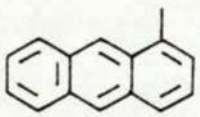
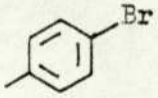
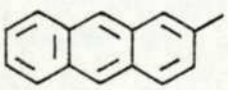
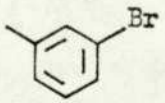
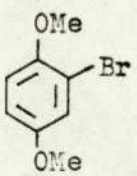
Table 1

REACTION	TEMP.°C	RATIO (221):(291)	ADDITION TIME/MINS	RATIO · (292):(291)[a]	YIELD(292) %	% (291) RECOVERED
a	25	1:1	40	3:1	24	8
b	-30	1:1	105	-	-	66
c	0	1:1	60	1:4	12	50
d	25	1:1	<1	6:1	35	5
e	25	6:1	<1	1:1.3	15	20
f	25	2:1	<1	-	31	-

a). Ratio obtained from p.m.r. spectra.

Slow addition of a 1:1 mixture of (221) and (291) to a solution of LiTMP in THF at 25° resulted in the formation of 1-methoxyanthracene (292) (24%). The product was contaminated with the starting bromide (291) (8%) and attempts to separate the mixture were unsuccessful. With lower reaction temperatures the yield of the anthracene (292) decreased, and, at -30°, none was formed and only (291) was recovered. The formation of benzyne is presumably too slow at such low temperatures and so the reactive species are not trapped. When the addition rate was greatly increased (<1 minute), then the yield of (292) was increased. A vast excess of benzocyclobutenol (221) appeared to hinder the reaction but with a 2:1 ratio of (221) : (291), a yield of 31% of pure 1-methoxyanthracene (292), m.p. 69.5-71°, was obtained.

Table 2

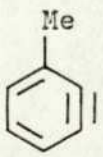
BENZYNE PRECURSOR	ANTHRACENE	YIELD %
 (293)	 (278)	20
 (294)	(278)	12
 (295)	 (296)	15
 (297)	 (298)	24
 (299)	(298)	19
 (226)	—	—

Having optimised the reaction with o-bromoanisole (291), the reaction was repeated with other substituted halobenzenes. The results are shown in Table 2.

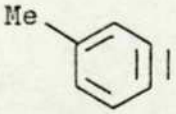
With bromobenzene (293), a 20% yield of anthracene (278) was obtained and, while this does not approach the excellent yields that Fleming[23] observed, it does reflect both the reactivity of the intermediates derived from benzocyclobutenol (221) and the near ideal conditions under which the reported anthracene synthesis took place.

The lower yield of anthracene (278) obtained with chlorobenzene (294) is consistent with the order of halide reactivity (Br > Cl) found by other workers[27] in the amination of halobenzenes with potassamide in liquid ammonia.

In reactions involving aryne intermediates, the direction in which the arynic bond forms[28] is important. When there are substituents ortho or para to the leaving group, one unique aryne forms. Thus o-bromotoluene (295) forms the benzyne (300) and thence 1-methylanthracene (296); similarly p-bromotoluene (297) gives (301) and thence 2-methylanthracene (298). When a meta group is present, the aryne bond may form in two different ways. Therefore m-bromotoluene (299) can form either of the benzynes (300) or (301). In such cases the more acidic



(300)



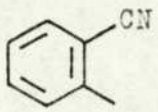
(301)

hydrogen is removed. In this case, the electron-donating methyl group favours removal of the p-hydrogen. Consequently the benzyne formed was (301) and thence 2-methylanthracene (298). None of the 1-isomer (296) was obtained.

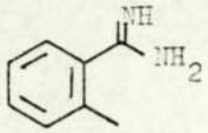
The absence of an anthracene product from the reaction involving 2,5-dimethoxybromobenzene is rationalized on the grounds of steric hindrance. Benzyne formation is too slow as the bulky amide base has difficulty in removing the C-6 proton due to the flanking bromo and methoxy groups.

When reaction f (Table 1) was repeated with o-tolualdehyde (213) in place of benzocyclobutenol (221), no 1-methoxyanthracene (292) was formed and only starting aldehyde (213) remained. Similarly, when a mixture of o-bromoanisole (291) and benzocyclobutenol (221) was stirred with sodamide in THF, no cyclic material was obtained. ^{1}H N.m.r. analysis of the reaction mixture showed that the alcohol (221) had been consumed and that the bromide (291) was the major material present. The above reactions give a further indication both of the ease of formation and of the reactivity of intermediates derived from the benzocyclobutenolate anion (285) and also the ease of benzyne formation obtained with the hindered amide base.

As a final example in this series, the nitrile (302) was available for study. Formation of the anion of o-tolunitrile (302), using potassamide or sodamide in liquid ammonia, has been shown by several workers to be a facile process[29,30,31]. The anion is remarkably stable in liquid ammonia and can be acylated[31] and alkylated[31], but if the solvent is changed to THF then the amidine (303) quickly forms.

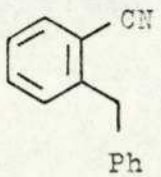


(302)

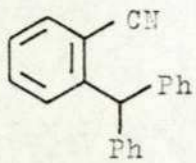


(303)

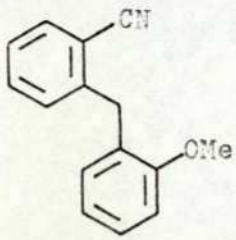
Dirstine and Bergstrom[29] have also shown that the anion can react with benzyne. Addition of a mixture of chlorobenzene, potassamide and liquid ammonia to a solution of the anion of (302) in liquid ammonia afforded the phenylated products (304) (32%) and (305) (9%). There was no report of any ring-closed material being formed. This observation was confirmed by repeating the reaction below. Sequential addition of



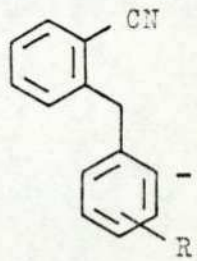
(304)



(305)



(306)



(307)

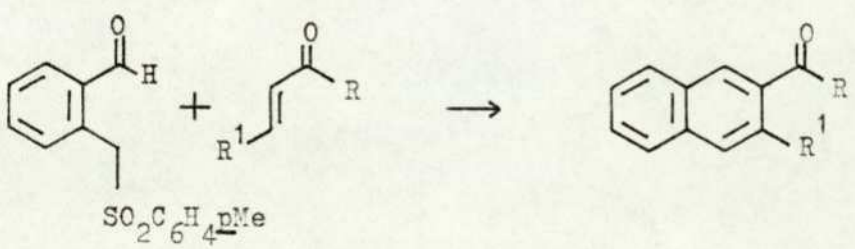
o-tolunitrile (302) and o-bromoanisole (291) to sodamide in liquid ammonia resulted in the formation of the nitrile (306) and no cyclized material was detected. Presumably, in liquid ammonia the anion (307) undergoes protonation rather than ring closure. Similar results have been obtained in the reactions of ketone enolates with benzynes. Leake and Levine[32], using liquid ammonia as solvent, obtained

ketones whereas Caubère, using an aprotic media, isolated other products (Scheme 31).

Clearly what was needed was a base/solvent that discouraged this feature of the reaction sequence, and, in view of the previous results, attention was turned to LiTMP/THF. In the event reaction of o-bromoanisole (291) and o-tolunitrile (302) with the amide base in THF at room temperature and at -30° did not result in the formation of phenylated or cyclized material. As attempts to alkylate the nitrile (302) were also unsuccessful, no further work was carried out with that system.

Recent work by Takahashi et.al[33] has shown that potassium t-butoxide/HMPA is a convenient medium for the condensation reaction of o- and p-tolunitrile with substituted benzaldehydes. In addition they report that if THF or DMF were used as solvents the reactions scarcely proceed.

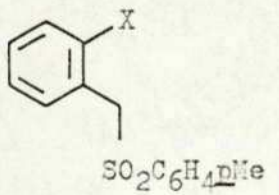
After this work was completed, there have been several reports of the preparation and reactions of toluate anions. Van Leusen et.al[34] found that on reaction with NaH in dimethoxyethane, the activated o-tolualdehyde derivative (308) formed a toluate anion which reacted with Michael acceptors to give, on work-up, the substituted naphthalenes (309) (Scheme 36).



(308) (309)

Scheme 36

The reaction was extended to the preparation of 1,2,3-tri-substituted naphthalenes by using the ketones (310), the ester (311) and the nitrile (312). Similarly the activating sulphone group could be replaced by sulphoxide or by nitrile.

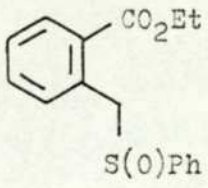


(310) X = COMe, COPh

(311) X = CO_2Et

(312) X = CN

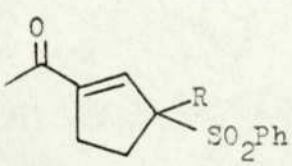
(313) X = NC



(314)

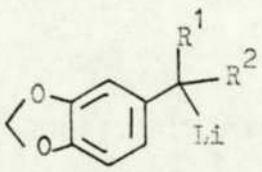
Hauser and Rhee[35] have independently prepared 1-hydroxy-2,3-di-substituted naphthalenes by reaction of the toluate anion of the sulphoxide (314) with Michael acceptors.

The sulphone group has also been used to promote the γ-alkylation of α,β-unsaturated ketones[36]. For example, methylation of the anion derived from the ketone (315) afforded the alkylated material (316)(62%) as the major product (7:1 ratio of γ : α-alkylation).



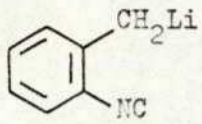
(315) R = H

(316) R = Me

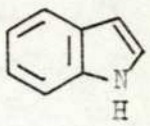


(311)

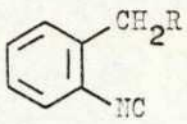
The toluate anions (311) undergo Michael addition to crotonolactone.[37] Both nitrile, ester and sulphoxide groups were used to activate the toluate system, but the dithiane derivative (311, $R,R^1 = -S(CH_2)_3-S-$) was found to be the most active.



(312)

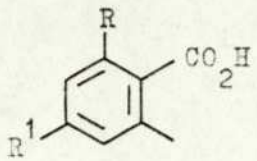


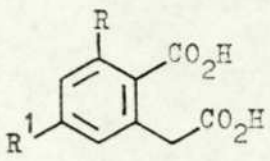
(313)



(314)

Whilst all the previously discussed toluate systems have required direct activation for anion formation, there are several notable exceptions. Saegusa *et.al*[38] have reported that reaction of *o*-tolyl isocyanide with two equivalents of LDA in diglyme at -78° gives the anion (312), which on warming to room temperature results in formation of indole (313). Alternatively low temperature reaction with alkyl halides, epoxides, ketones or aldehydes affords the derivatives (314). Also the anion (312) also undergoes conjugate addition with *α,β*-unsaturated ketones, yet Van Leusen et.al[34] obtained only indoles when they used the isonitrile (313) in their reaction sequence. The above observations indicate that the anion (312) could not be used in the afore-mentioned benzyne reactions. An *o*-acid moiety has been shown to enhance toluate anion formation[40,41]. For example generation of the dilithium anion of an *o*-toluic acid (315) in the presence of an excess of LDA in THF followed by acylation with dimethyl carbonate affords, on work-up, the corresponding homophthalic acid (316) (80-90%). Whitlock *et.al*[42] have shown that, on treatment





(315a) R = R^1 = H

(315b) R = OMe. R^1 = H

(315c) R = R^1 = OMe

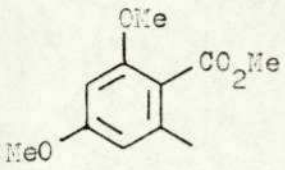
(316a) R = R^1 = H

(316b) R = OMe, R^1 = H

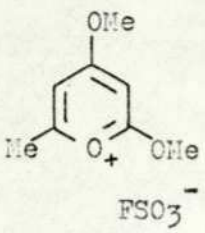
(316c) R = R^1 = OMe

with strong base, o-bromophenylalkenoic acids are cyclised to benzocycloalkenones (cf. Scheme 13). Thus, the above work has indicated that the dianion of o-toluate acids should be capable of undergoing reaction with benzynes and that any intermediate aryl lithium species could undergo ring closure.

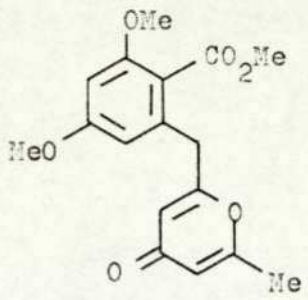
Staunton and Leeper[43] have reported that the methyl ester (317) generates a toluate anion on treatment with LDA in THF and further reaction with the pyrylium salt (318) affords the pyrone (319) in 25-35% yield. This increased reactivity of the toluate anion would appear to be due to the methoxy substituents since attempts to repeat the pyrone synthesis with methyl toluate (277) were unsuccessful[44]. Therefore, Staunton's work has shown that a stable o-toluate anion can be generated from a toluate ester and that these anions could be used in an annulation sequence involving benzynes. Furthermore, the extension to other methoxy substituted derivatives, for example o-tolualdehyde derivatives, or the activated systems (310), (311) or (312) would be of interest.



(317)



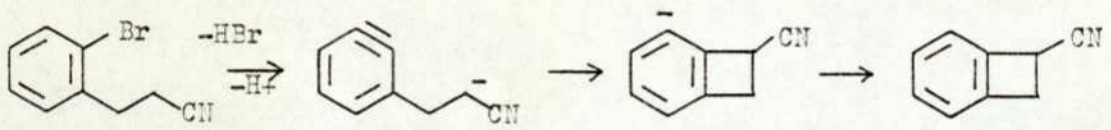
(318)



(319)

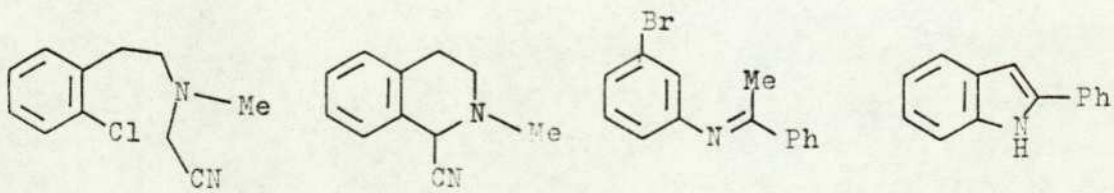
Intramolecular Cycizations

The formation of benzocyclic systems by aryne cyclizations is well documented[45]. Both carbocyclic and heterocyclic compounds have been prepared by the reaction of a side-chain nucleophile with the aryne function. An example of the former is the synthesis of benzocyclobutenes (Scheme 37) developed by Bunnett and Skorez[46] and later extended to substituted derivatives by Kametani and Fukomoto[47].



Scheme 37

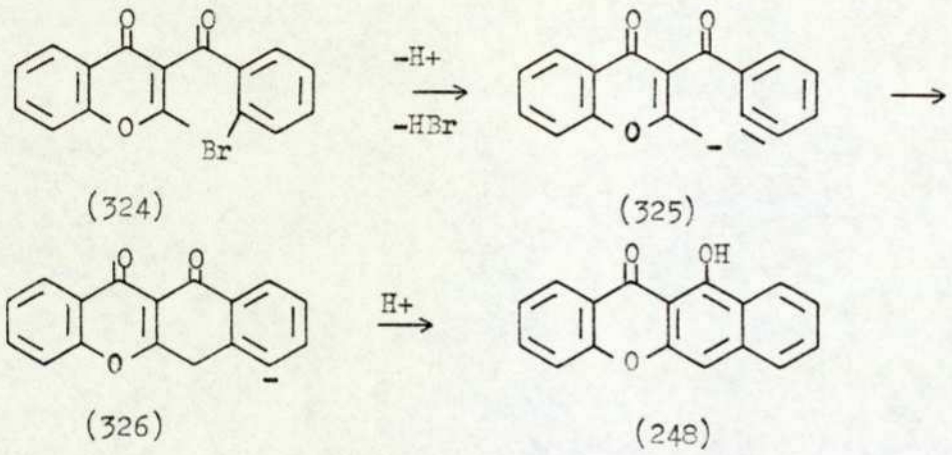
Other workers have prepared benzoheterocycles via a similar route[48]. For example, compound (320) was cyclized to the tetrahydroisoquinoline derivative (321) using metal amide in liquid ammonia[49] and substituted indoles (eg. (323)) have been prepared by the action of sodamide/sodium t-butoxide in THF on compounds of type (322)[50].



(320) (321) (322) (323)

Benzoxanthenone Synthesis

The application of this sequence to the preparation of the benzoxanthenone nucleus (Scheme 38) should have several advantages over the intermolecular approach. The increased stability of the chromone (324) over the 3-carboxy derivative, together with the possibility of rapid intramolecular reaction of both reactive species, might be expected to enhance reaction.



(324) (325) (326) (248)

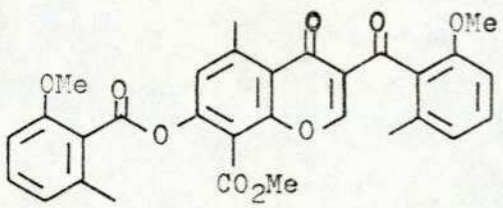
Scheme 38

The required chromone (324) was prepared in good yield using the general procedure outlined in Scheme 27, starting from o-hydroxyacetophenone (249) and o-bromobenzoyl chloride.

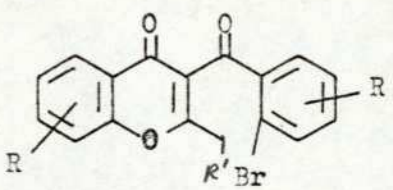
Reaction of the chromone (324) with an excess of LiTMP in THF gave the required benzoxanthenone (248) in 19% yield, together with 44% of recovered starting material. When the reaction was repeated using sodamide in liquid ammonia, only the benzoxanthenone (248), 33%, was

isolated. As both base/solvent are known readily to form benzynes from halobenzenes, it is proposed that the reaction proceeds *via* the anion-aryne intermediate (325) as shown in Scheme 38.

The application of this sequence to the chromone (324) represents a significant synthetic manoeuvre as it should now be possible to prepare substituted benzoxanthenones. Previously, Wallace[3] had tried to synthesise such systems by photoenolisation. Attempted irradiation of the derivative (327), however, was ineffective, the compound being stable to both short and long wavelength U.V. irradiation.

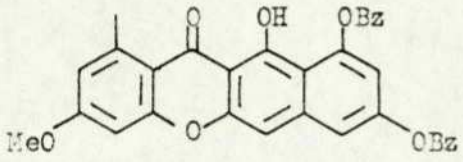


(327)

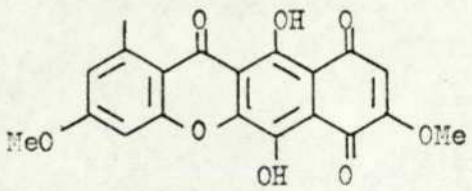


(328)

A possible extension of the aryne procedure could involve the functionalised chromone (328), where R = carboxy, protected hydroxy *etc.* and the presence of an electron-withdrawing substituent, R^1, would enhance both the formation and stability of the resulting anion. Kato and his co-workers[51] have recently reported an inefficient synthesis of the benzoxanthenone (329) and have transformed the material into Bikaverin (330)[52].



(329)

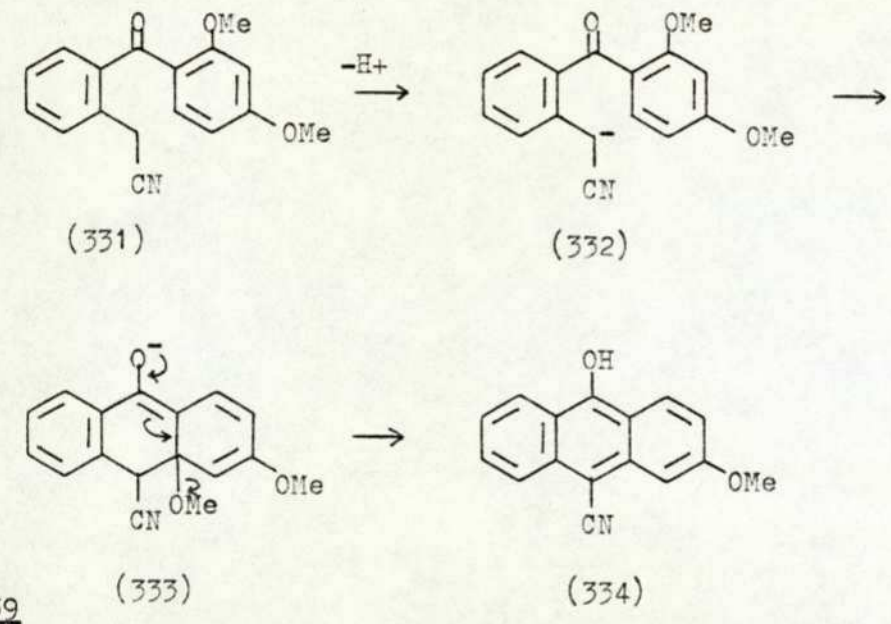


(330)

Anthracene Synthesis

Encouraged by the successful benzoxanthenone synthesis, we investigated the possibility of using the process to prepare some anthracene derivatives from substituted benzophenones.

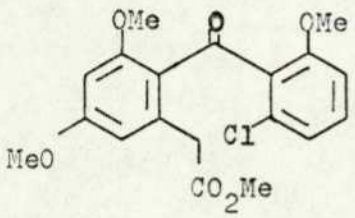
The literature revealed that a similar sequence had been developed by Hassall and co-workers[53]. The example shown in Scheme 39 was taken from the initial investigations and shows the conversion of the benzophenone (331) to the anthrol (334).



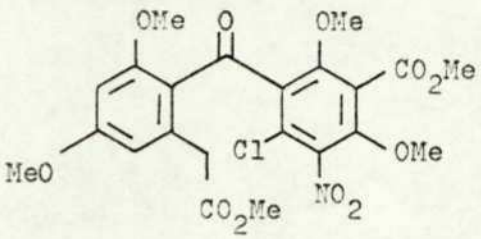
Scheme 39

More recent work[54] with highly substituted derivatives showed that the cyano group could be replaced by carbomethoxy, that the procedure was successful with benzophenones substituted with electron with-drawing groups and that regiospecificity could be achieved by preferential displacement of chloride ion; e.g. (335) failed to cyclise whereas (336)

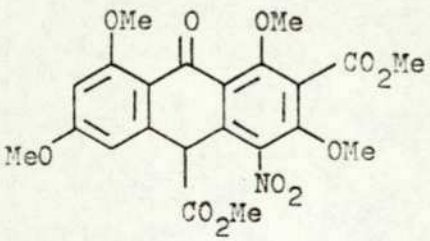
afforded (337).



(335)

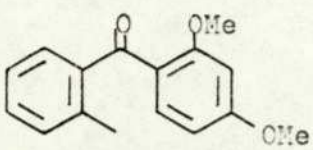


(336)



(337)

Wallace[3] had also attempted some similar reactions. Attempts to emulate Hassell's reaction with the benzophenone (338) failed. With the chromone (339), however, the activating influence of two carbonyl groups together with the presence of a suitable leaving group combined to promote rearrangement to the naphthol (340).



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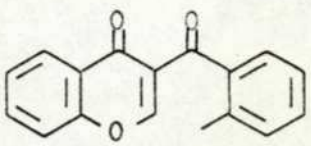
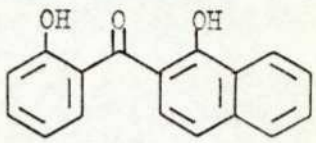
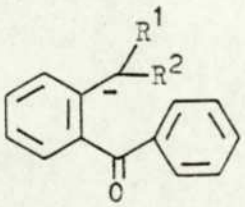


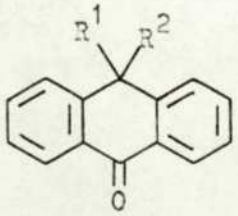
(339)



(340)



(268)

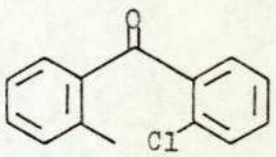


(276)

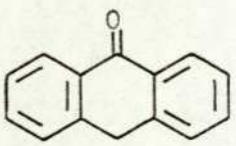
Caubère[17] had also proposed that the formation of the anthrone (276) occurs *via* the anion (268) (Scheme 33).

The above results were most encouraging. The aryne-anion cyclisation is a facile reaction and also this sequence, unlike Hassall's and Caubère's reactions, would not involve the disruption of the aromatic sextet.

In this brief study, 2-chloro-2'-methylbenzophenone (341) was used as the model system, with the expected cyclisation product being anthrone (280). Unfortunately the results obtained were both disappointing and somewhat perplexing.



(341)



(280)

Treatment of the benzophenone (341) with sodamide in liquid ammonia resulted in no cyclisation and the starting material was recovered in good yield. With LiTMP in THF, however, a deep red solution was obtained, but the required cyclisation product (280) could not be detected. The majority of the material was of a polar nature and afforded an indistinct ^{1}H n.m.r. spectrum.

It is interesting to compare the reaction conditions used by the afore-mentioned researchers. Hassalls[153] conditions were initially NaOMe/DMSO at 140° (Scheme 39) and in later work KOBu^{t}/DMF at either 90° or, for more activated systems such as (336), room temperature. Wallace[3] used

LDA in THF. Even at reflux temperature the benzophenone (338) failed to cyclise, whereas the chromone (339) reacted at room temperature. Caubère[17], using sodamide in THF, found that a reaction temperature of 45° was necessary to obtain any appreciable amounts of the anthrone (276).

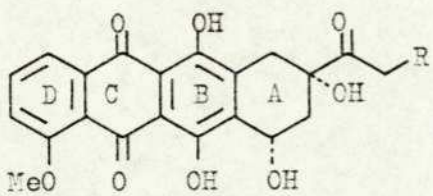
Whilst the above results are by no means conclusive, there is an indication that the reactivity in this 2-alkylbenzophenone system is dependent on the formation of the toluate anion. In the benzophenones (338) and (341), the o-carbonyl substituent is not sufficient for anion formation and either direct, as in (331), or indirect, as in (339), activation is necessary.

The formation of the anthrone (276) appears to contradict the above comments, but the anion (268), from which, according to Caubère,[17] (276) is derived, was not prepared directly from a toluate species. It was, however, obtained from a benzocyclobutenol derivative and it has been shown that the anions derived from these derivatives have a much greater reactivity than their toluate counterparts.

Phthalide Studies

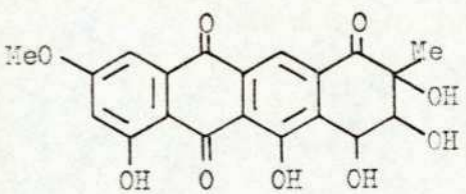
Introduction

The literature reviewed in the preceding pages of this volume shows that the anthracyclinones are a most interesting and pharmaceutically promising chemical system. A great amount of effort has been put into both the total synthesis and modification of these compounds, and in particular daunomycinone (342a) and adriamycinone (342b)



(342a) R = H

(342b) R = OH

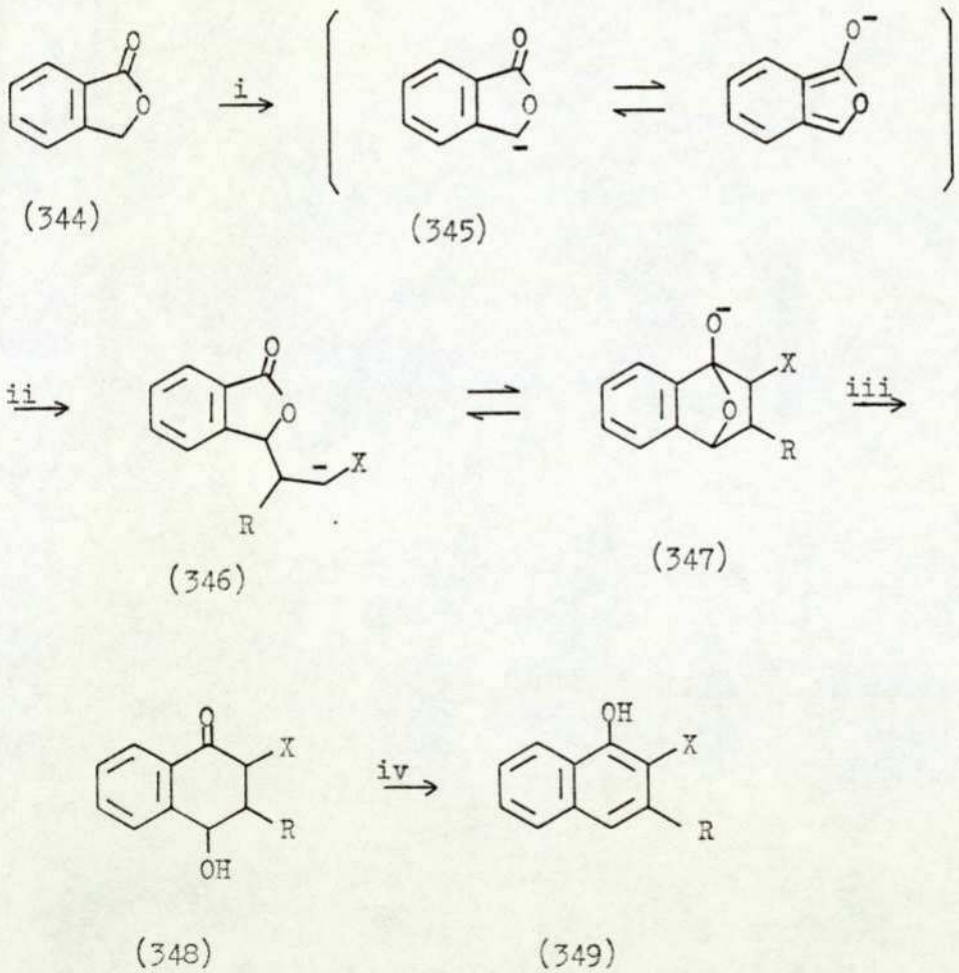


(343)

The main problems in this area of cancer chemotherapy are the cardiotoxic effects and the lack of knowledge of the basic mode of action of the anthracycline antibiotics. Once the structure-activity relationships have been defined then the design of more active drugs will commence, and these compounds will, no doubt, contain modifications in both the aromatic system (rings DCB) and also in ring A. The most attractive routes to the compounds are not very flexible because of the

limitations in the nature of substituents and substitution pattern in the starting materials. Most of the new anthracyclines that have been tested, have been prepared from the natural material by modification of either the glycoside or the acetyl grouping. Therefore, there is a need for new routes to simple aromatic starting materials.

Interest in the formation and reactions of dienolate and related benzylic anions led to an examination of the reactions of phthalide (344) and a route to substituted 4-hydroxytetralones (348) was envisaged (Scheme 40). Reaction of the phthalide anion (345) with a Michael acceptor

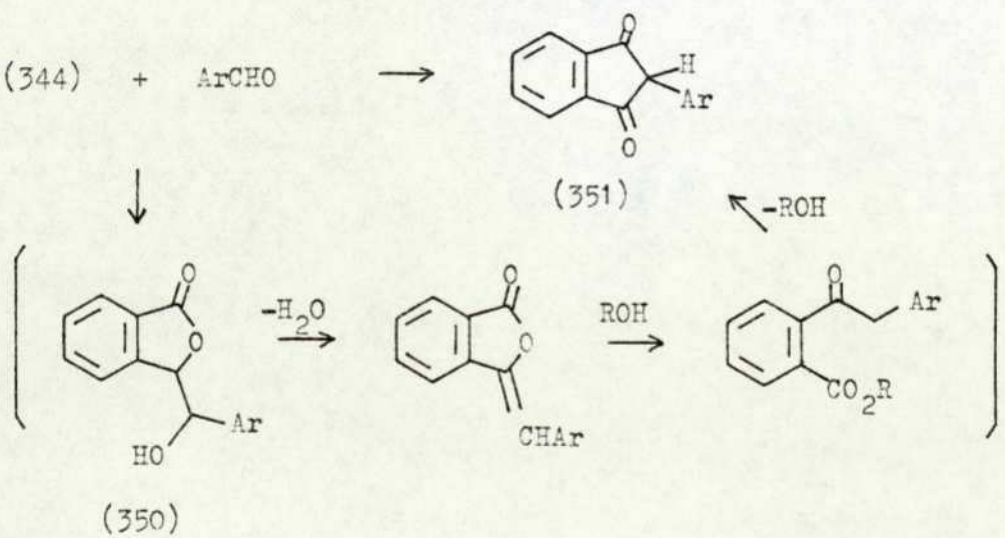


(344) (345) (346) (347) (348) (349)

Scheme 40 Reagents: i, Base ; ii, RCH=CHX, aprotic solvent; iii, H_3O^+ ; iv, Acid catalysed dehydration.

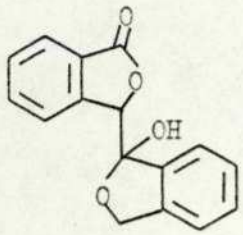
could give the adduct (346), which, under aprotic conditions, would cleave the lactone to afford the tetralone system (348) rather than the substituted phthalide. Comparison of the system (348) with the basic anthracyclinone structure, and especially steffimycinone (343), shows that the system (348) has potential ring A character and a number of reactive centres. Furthermore, the tetralone system (348) should undergo dehydration to the naphthol derivative (349). With these heuristic thoughts in mind, the work to be described was undertaken.

Examination of the literature revealed a paucity of information about phthalide anions. When phthalide (344) is treated with sodium methoxide in methanol, the resulting yellow solution of the anion (345) is capable of undergoing condensation reactions with aromatic aldehydes. This reaction has been used in the preparation of 2-substituted-1,3-indanones[55,56,57] (351) (Scheme 41). Although initial attempts at preparing the intermediate benzalphthalide (350) were unsuccessful, the use of lower temperatures and shorter reaction times led to its isolation[56,57]. If potassium t-butoxide in dimethyl suphoxide were used as the medium, the resulting anion underwent self-condensation, giving

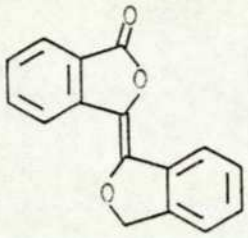


Scheme 41

rise to either the alcohol (352) or the dehydration product (353) depending on the reaction temperature[58].



(352)



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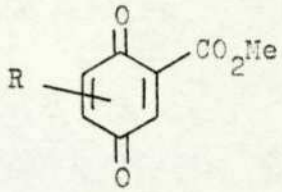
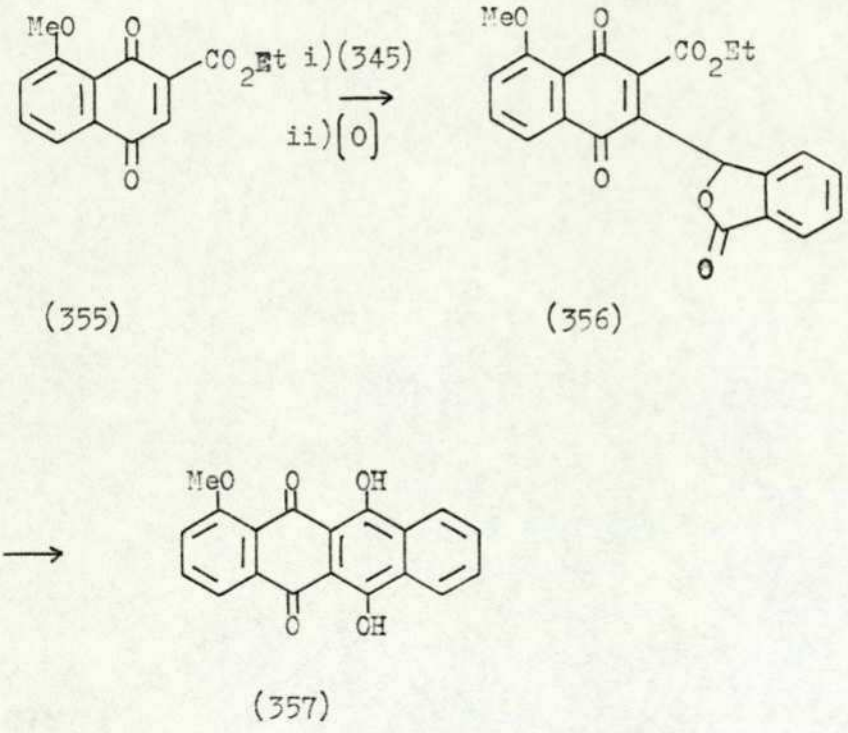


(354)

Early work by Eugster et.al.[59] showed that the anion (4) was capable of reacting with the substituted benzoquinones (354) and the sequence was developed[60] to afford a preparation of hydroxysubstituted naphthacenequinones. For example, reaction of the anion (4) with the quinone (355) gave the adduct (356) (26%), which, on treatment with strong acid, cyclized to the naphthacenequinone (357) (27%) (Scheme 42). Although this sequence has limited synthetic use, Eugster's work had shown that the anion (345) was capable of undergoing 1,4-addition to conjugate systems.



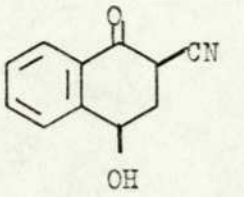
(355) (356)

(357)

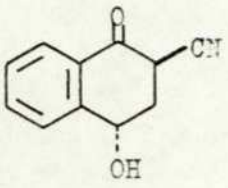
Scheme 42

Additions to Michael acceptors

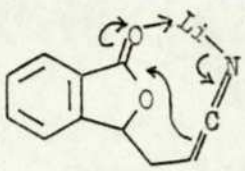
Treatment of phthalide (344) with lithium diisopropylamide in THF at -40° generated the orange carbanion (345). Addition of acrylonitrile (358) resulted in loss of colour together with the formation of a viscous solution or suspension. Acid work-up and ethereal extraction followed by preparative chromatography of the crude reaction mixture afford a solid (39%), identified as 2-cyano-4-hydroxytetralone (359). The infra-red spectrum showed the presence of the hydroxy, cyano and aryl ketone groups and accurate mass measurements confirmed the molecular formula as $C_{11}H_9NO_2$. The p.m.r. spectrum revealed that (359) was a 1:1 mixture of epimers. The signals due to the C-2 protons appeared as double doublets δ3.82 (J = 5,15Hz) and at δ4.36 (J = 6.5,12Hz) for each epimer. By virtue of the large vicinal coupling constant, the C-2 proton in both epimers was assigned the pseudoaxial orientation. The cyano group is therefore in a pseudoequatorial orientation and this is consistent with the known preference for large substituents in tetralin systems to adopt the equatorial conformation[61]. On D_2O exchange, the C-4 proton multiplet at δ4.92-5.16 sharpened to a broad multiplet of $W_{\frac{1}{2}}$ 11Hz and a sharper multiplet of $W_{\frac{1}{2}}$ 4Hz was also observed slightly downfield. In daunomycinone the corresponding benzylic proton is in the pseudoequatorial orientation and has a $W_{\frac{1}{2}}$ value of 7Hz,[62] whereas other anthracyclinones, epimeric at this position have $W_{\frac{1}{2}}$ values of 13-17Hz.[63] Thus the two epimers have the structures (380) and (381) but chemical or physical separation was not possible.



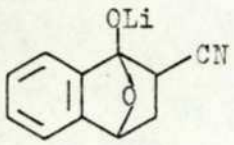
(380)



(381)



(382)

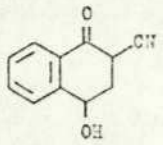
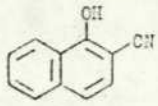
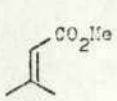
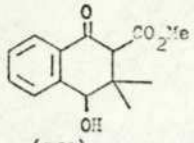
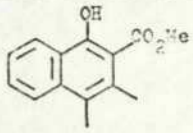
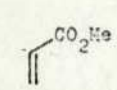
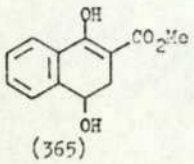
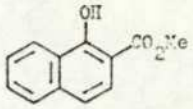
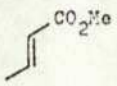
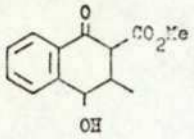
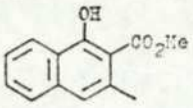
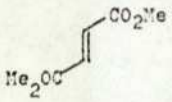
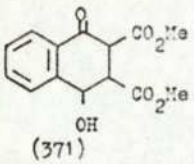
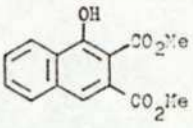
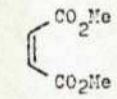
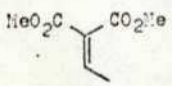
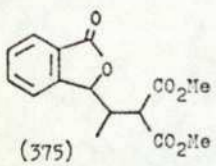
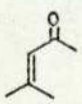
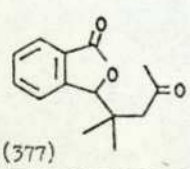
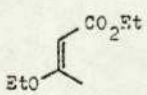


(383)

The probable course of the reaction is as outlined in Scheme 40 and transition states of the type (382) and (383) are envisaged[64]. Further confirmation of the structure came from the dehydration of the tetralone (359) with neat trifluoroacetic acid to give 2-cyano-1-naphthol (360) (74%), a known compound.

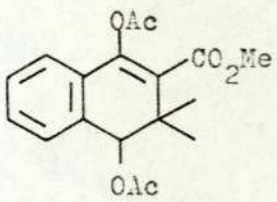
Using the procedure previously described, the anion (345) was reacted with other Michael acceptors and the results are shown in Table 3.

Table 3 : Results of Tetralone and Naphthol Syntheses from phthalide (344)

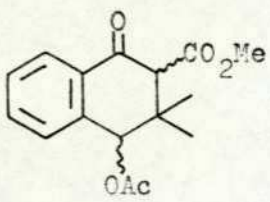
Michael Acceptor	Product[a]	Yield %	Naphthol	Yield %
 (358)	 (359)	39	 (360)	74
 (361)	 (362)	37	 (363)	65
 (364)	 (365)	37	 (366)	72
 (367)	 (368)	48	 (369)	68
 (370)	 (371)	44	 (372)	78
 (373)	(371)	44	(372)	82
 (374)	 (375)	45	——	
 (376)	 (377)	20	——	
 (378)	——			
 (379)	——			

[a] as isomeric mixture

When the reaction was repeated with methyl 3-methylcrotonate (361), the derived tetralone (362) was isolated as an unstable viscous yellow oil. The p.m.r. spectrum of the material showed a 2:1 epimer ratio with the signals belonging to the C-4 and C-2 protons occurring as singlets at δ4.64 and δ4.00 in the major epimer and at δ4.62 and δ3.52 in the minor. Acylation of the mixture with pyridine and acetic anhydride afforded two products. The more polar material was identified as the enol acetate (384), (15), and p.m.r. spectroscopy showed that the less polar material was a 2:1 mixture of the epimeric acetates (385) (56%) with the C-4 protons occurring as singlets at δ5.92 and δ6.12[65].

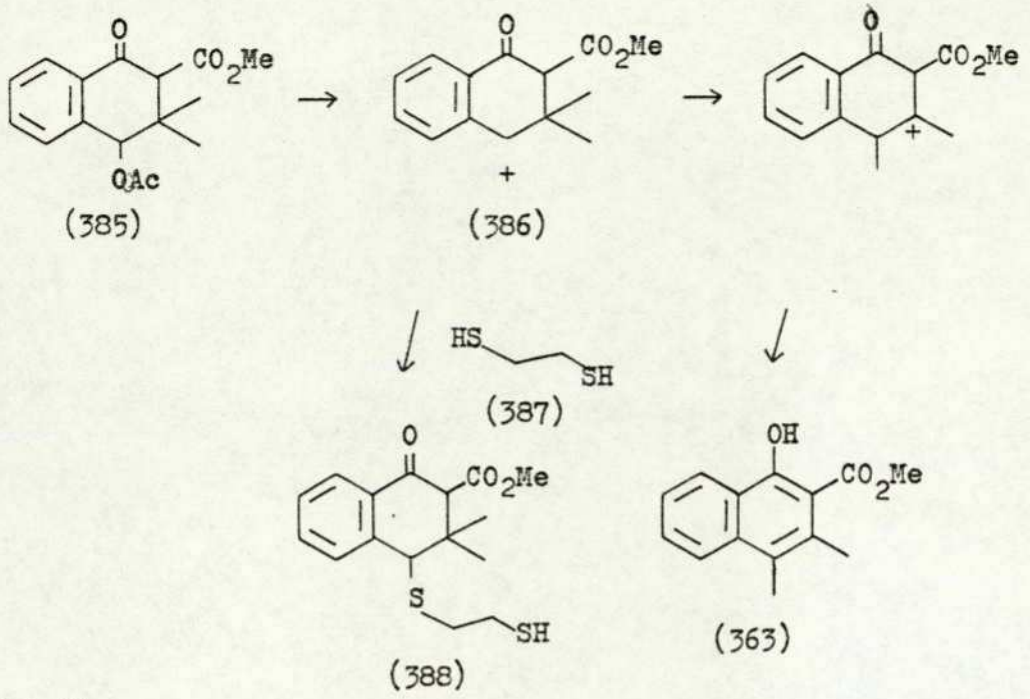


(384)



(385)

On treatment with either boron trifluoride etherate in dichloromethane or toluene-p-sulphonic acid in benzene at reflux temperature the tetralone (362) underwent dehydration with concomitant methyl migration to give the naphthol (363). If the reaction was repeated with the acetate (385) and in the presence of ethane-1,2-dithiol (387) the intermediate carbonium ion (386) was trapped and the 4-thiosubstituted tetralone (388) was isolated together with some of the naphthol (363) (Scheme 43). The overall yield of the naphthol (363) from phthalide (344) was 29%. If, however, the intermediate tetralone (362) was not isolated, but the crude



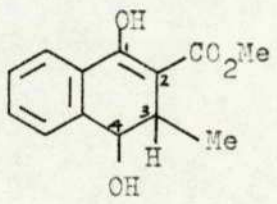
Scheme 43

reaction mixture treated with a Lewis acid, then the yield of naphthol (363) was increased to 35%.

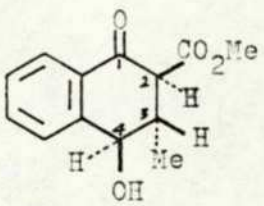
2-Carbomethoxy-4-hydroxytetralone, prepared from methyl acrylate (364), was found to exist entirely in the enolic form (365) and, on acid catalysed dehydration, the known naphthol (366) was obtained in good yield.

In order to examine the preferred orientation of 3-substituents in the tetralone system, compounds (368) and (371) were prepared. Spin decoupling p.m.r. experiments showed that the methyl derivative (368) was obtained as a 1:1 mixture of enol (389) and keto (390) isomers. In the enol (389), irradiation at the frequency of the C4-H, singlet ($W_{\frac{1}{2}}$ 5Hz) at δ 4.40 resulted in the collapse of the C3-H multiplet at δ 2.98 - 3.18 to a quartet (J = 6.5 Hz). Whereas in isomer (390), irradiation at the frequency of the C3-H multiplet at δ 2.38 - 2.81 caused collapse of the methyl doublet, the C2-H doublet at δ 3.28 (J = 13 Hz), and the C4-H broad singlet at δ 4.68 ($W_{\frac{1}{2}}$ 10 Hz). By virtue of the vicinal coupling constant of 13 Hz between C2-H and C3-H and a half-peak width of 10 Hz

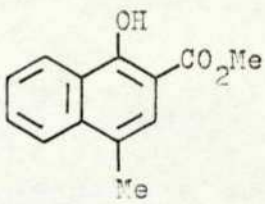
substituents at
for C4-H, it is proposed that the C2, C3 and C4 in (390) adopt the preferred pseudoequatorial orientation[61].



(389)



(390)

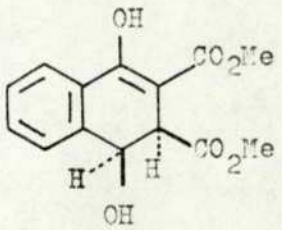


(391)

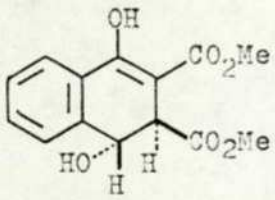
Again, separation of the isomers was not possible but the mixture was smoothly converted into the naphthol (369) on brief treatment with acid. The naphthol (369), m.p. 84-6°, analysed correctly for $C_{13}H_{12}O_3$ and had spectral data consistent with the proposed structure. The isomeric 2-carbomethoxy-4-methyl-1-naphthol (391) which could arise from a methyl migration in the intermediate carbonium ion (c.f. Scheme 43), whilst agreeing with the analytical and spectral data, can be discounted as it is a known compound of m.p. 109-110° [66].

The p.m.r. spectra of the carbomethoxy derivative (371), obtained from the reaction with dimethyl fumarate (370), showed that half of the product was in the enolic form and the presence of two exchangeable singlets at δ12.40 and δ12.44 indicated that there were two enolic epimers. Furthermore, on irradiation at the frequency of the broad C4 proton signal at δ5.04, the C3 proton doublets of epimers (392) and (393) at δ4.06 (3Hz) and δ3.94 (6Hz) collapsed. It was not possible to deduce

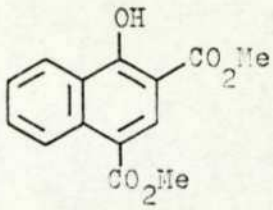
the orientation of the carbomethoxy substituents in the tetralone (371) as the signals due to the C2 and C3 protons were obscured. In the case



(392)



(393)



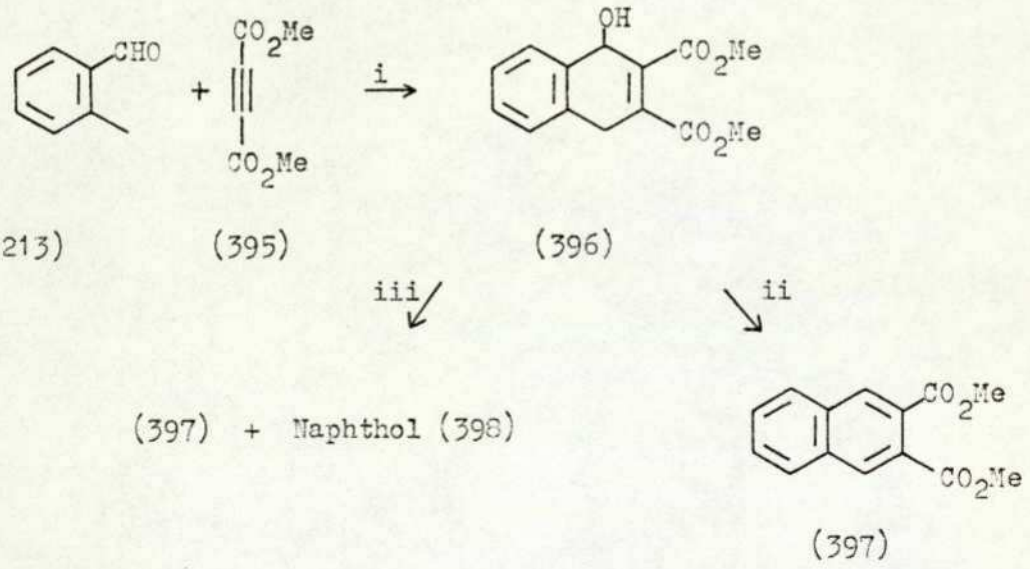
(394)

of the adduct (371), obtained from dimethyl maleate (373), half of the material was again in the enolic form but only one of the enol isomers was present (δ 4.06(d,J = 3Hz), 12.46 (s, exch.)). In both cases separation of the mixture (371) was not possible, but the infra-red spectra were essentially the same and accurate mass measurements supported the molecular formula $C_{14}H_{14}O_6$.

Dehydration of either adduct afforded, in good yield, a naphthol m.p. 102-3° which was assigned the structure (371) on the basis of the following data. ν_{max} 3400-3000, 1720, 1685cm^{-1}. δ 3.88 (3H,s); 3.92 (3H,s); 7.36 (1H,s, C4-H); 7.42-7.70 (3H,m); 8.22-8.38 (1H,m, C8-H); 11.68 (1H,s,exch.,). Accurate mass and analytical data confirmed the molecular formula $C_{14}H_{12}O_5$. The known isomeric 4-carbomethoxy derivative (394), m.p. 144,[67] can be discounted.

The naphthol (372) has been reported[68] to have been prepared from 2,3-dicarbomethoxy-1,4-dihydronaphthol (396) (Scheme 44) but the material isolated had different physical and spectral data to that obtained for (372).

Oxidation of the dihydronaphthol (396) with manganese dioxide gave the known naphthalene (397) as the major product, together with a 10-20%



(213) (395) (396)

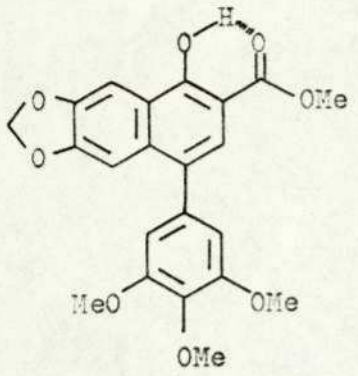
(397) + Naphthol (398)

(397)

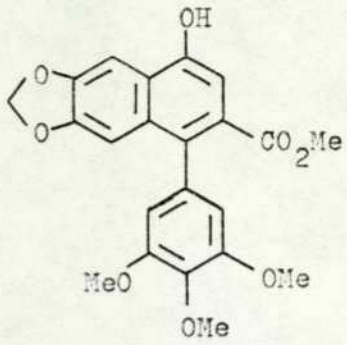
Scheme 44 Reagents: 1, hν ; ii, p-TsOH,xylene, Δ ; iii, MnO_2, ⌀H, r.t.

yield of a naphthol (398) (assigned structure (372)) m.p. - 145-160(decomp), ν_{max} 1730, 1665cm^{-1}. δ (60 MHz) 3.30 (3H,s); 3.84 (3H,s); 7.20-7.60 (4H,m); 8.40-8.50 (1H,m); 12.23 (1H,s, exch.). The material analysed correctly for $C_{14}H_{12}O_5$.

The absence, in the infra-red spectrum of hydroxyl absorption is not unusual in these systems and can be attributed to the very high degree of hydrogen bonding between the phenolic hydrogen and the adjacent carbomethoxy group. Many of the naphthols shown in tables 3 and 4 do not exhibit hydroxyl absorptions in the infra-red spectra. A similar situation has been reported by Genster et.al[69] who observed that the naphthol (399) showed no distinct hydroxy absorption, in contrast to isomer (400) (ν_{max} 3350cm^{-1}).Of note in the p.m.r. spectrum of the naphthol (398) was the



(399)

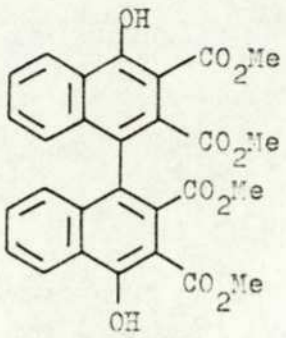


(400)

high field carbomethoxy signal at δ 3.30 and the lack of a sharp singlet in the aromatic region expected for the C4-proton.

In order to resolve this dichotomy, a fresh sample of the naphthol (398) was prepared by the literature method[68]. Recrystallization from benzene afforded pure (398) m.p. 240-6 dec. The infra-red spectrum was as reported, but the p.m.r. spectrum (100 MHz) was found to differ in the aromatic region - the multiplet at δ7.2-7.6 possessed an integrated intensity appropriate to <u>three</u> and not four protons. The naphthol (398) analysed correctly for $C_{28}H_{22}O_{10}$ and this formula was confirmed by accurate mass measurements. Thus the naphthol obtained by Mellows[68] from the oxidation of the dihydronaphthol (396) does not have the structure (372) but is the dimeric compound (398). Attempted formation of (398) by manganese dioxide oxidition of the naphthol (372) proved abortive.

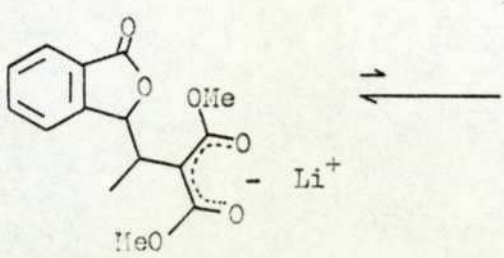
The reaction between dimethyl ethylidenemalonate (374) and the phthalide anion (345) afforded a light yellow oil, identified as the substituted phthalide (375). From the infra-red spectrum it was apparent that the material isolated was not a 4-hydroxytetralone derivative, since,



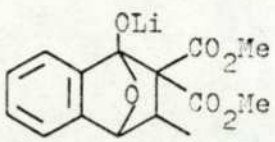
(398)

in the I.R. spectrum, no hydroxy and aryl ketone absorptions were present but absorptions were observed at 1755 and 1730cm^{-1}, as required for structure (375). The p.m.r. spectra and spin decoupling experiments were consistent with a 2:1 mixture of the epimers of (375). Mass spectrometry confirmed the molecular formula as $C_{15}H_{16}O_6$.

As previously stated, transition states of the type (401) and (402) are envisaged in the cyclization, but, presumably in this case, the resulting adduct (401) is too stable an entity to open the lactone ring, consequently on protonation the phthalide (375) and not the tetralone (403) was obtained.

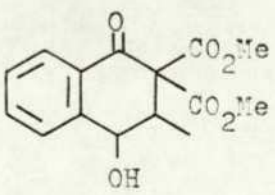


(401)



(402)

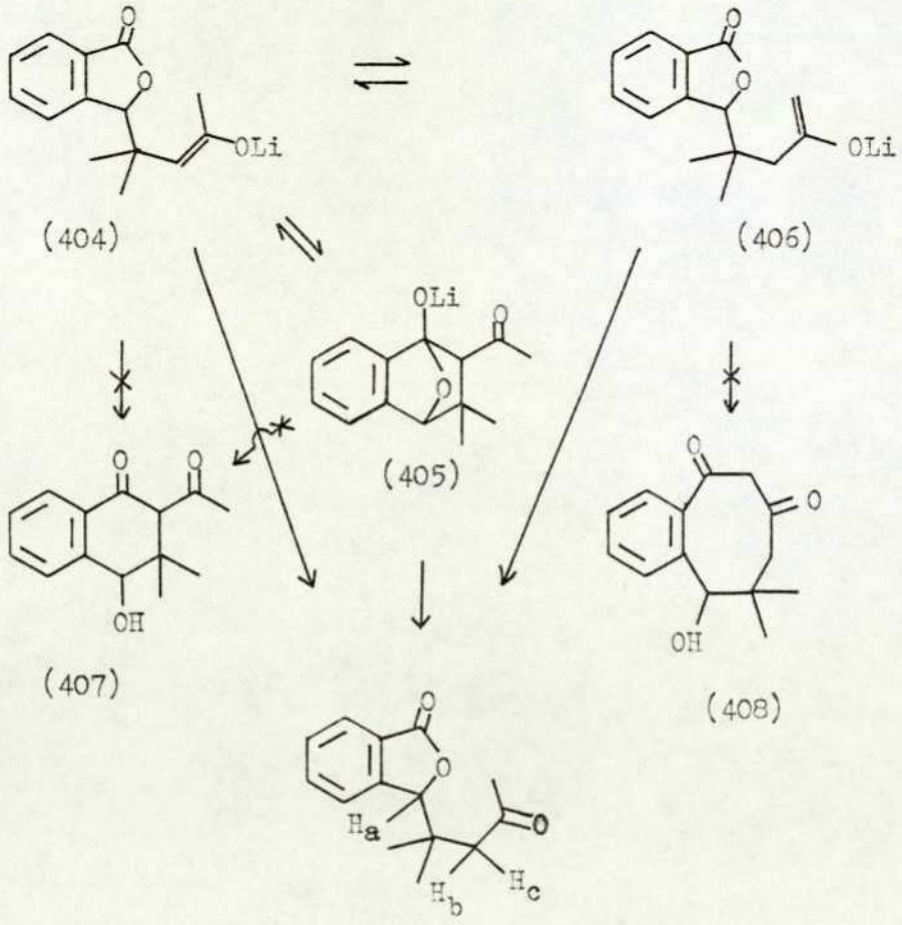
(375)



(403)

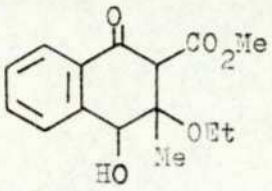
A similar result was obtained with mesityl oxide (376). An unstable yellow oil was isolated from the reaction mixture and was assigned structure (377) on the basis of the spectral data. Of note in the p.m.r. spectrum were signals corresponding to H_b and H_c, δ 2.48 and 2.90 (2H, centres of ABq, J = 18Hz), and H_a, δ 5.97 (1H,s). The lack of ring closure is of interest. Presumably the reaction proceeds <u>via</u> (404) and either this intermediate, or (406), is either unable to cleave the lactone ring system, or that it forms an intermediate (405) which collapses with retention of the lactone ring. No evidence for the formation of compounds (407) and (408), resulting from ring closure, was obtained.

It was hoped that ethyl 3-ethoxycrotonate (378) would be a Michael acceptor of great potential since the resulting adduct (409) would have

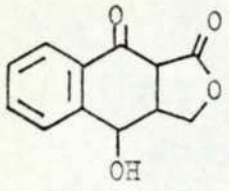


(404) (406) (405) (407) (408) (377)

a ring A system of the type found in steffimycinone (343) and, furthermore, there existed the possibility of subsequent transformation to substituted quinone/quinol systems. In the event, the crotonate (378) proved to be a poor Michael acceptor and neither the initial adduct nor the cyclized material (409) was observed.



(409)



(410)

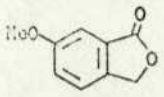
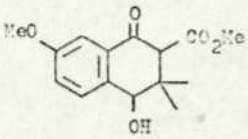
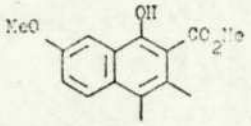
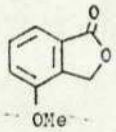
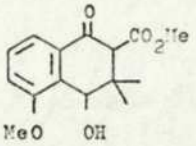
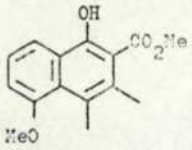
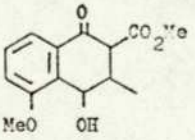
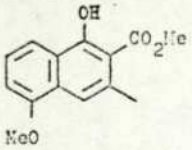
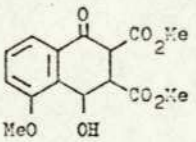
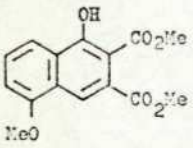
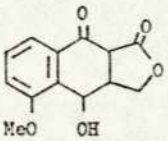
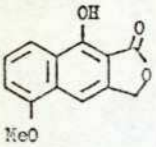
Attempts to prepare the lactone (410), a compound that could be used for further aromatic ring homologation, were unsuccessful. Even though, on addition of crotonolactone (379), to the anion (345), a change in the colour of the reaction mixture occurred, none of the expected tetralone (410) nor the initial adduct could be isolated.

As linear polynuclear phenolic systems are a structural feature present in many antibiotics and other natural products, attempts were made to extend the reaction to include some substituted phthalides (Table 4).

A small amount of 6-methoxyphthalide (411) was prepared in low yield from m-methoxybenzoic acid[70]. On treatment with lithium diisopropylamide in THF at -40°, (411) formed an orange anion which reacted with methyl 3-methylcrotonate (361) to give the tetralone (412), 41%, as a yellow viscous oil. The infra-red spectrum and accurate mass data were in agreement with the proposed structure and, as previously experienced with the demethoxy derivative (362), the p.m.r. spectrum of (412) showed a 2:1 epimer ratio. On brief treatment with Lewis acid, the tetralone (412) underwent dehydration with concomitant methyl migration to give methyl 3,4-dimethyl-1-hydroxy-7-methoxy-2-naphthoate (413).

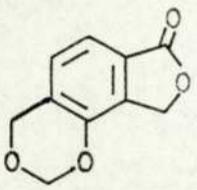
Buehler et.al[71] have reported that the condensation of formaldehyde and 4-hydroxybenzoic acid in acid media produces chiefly two compounds melting at 175° and 254°. The latter compound was unambiguously shown[71] to be 4-hydroxyphthalide, which was methylated to give 4-methoxyphthalide (414). However the structure of the former compound was not determined. In the preparation of the phthalide (414), the unknown material was isolated as white feathers, m.p. 177-9° (from water). A molecular formula of $C_{10}H_8O_4$ was obtained from accurate mass data and the infra-red spectrum showed the presence of a 5-ring aryl lactone (ν_{max} 1740cm^{-1}). The p.m.r. spectrum, recorded in hexadeuterioacetone, showed the following resonances:- δ 5.20 (2H,s), 5.34 (4H,s), 7.18 (1H,d, J = 8Hz), 7.46 (1H, d, J = 8Hz).

TABLE 4

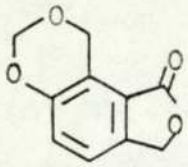
PHTHALIDE	"MICHAEL ACCEPTOR"	PRODUCT[a]	YIELD %	NAPHTHOL	YIELD %
 (411)	(361)	 (412)	41	 (413)	51
 (414)	(361)	 (415)	48	 (416)	53
(414)	(367)	 (417)	58	 (418)	43
(414)	(373)	 (419)	34	 (420)	67
(414)	(379)	 (421)	30	 (422)	52

[a] as isomeric mixture

From the above spectral data it was concluded that the unknown compound is either the lactone (423) or the isomer (424). Attempts to differentiate by spectroscopic means between the two structures were unsuccessful.



(423)



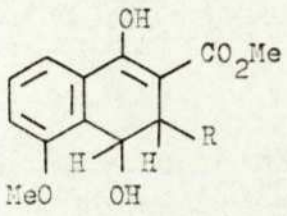
(424)

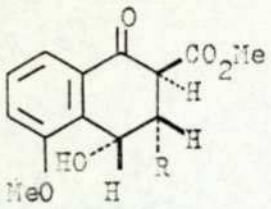
When 4-methoxyphthalide (414) was treated with the amide base at low temperatures, a green colour quickly developed. Quenching of this anion with methyl 3-methylcrotonate (361) afforded the tetralone (415). The p.m.r. spectrum of this 5-methoxy derivative (415) showed that only one of the epimers had been produced, unlike the results obtained for the related systems (362) and (412). On treatment with acid the tetralone (415) underwent dehydration and methyl migration to give the naphthoate (416).

Further evidence that the methoxy group was exerting an effect on the reaction was obtained on examing the p.m.r. spectra of the tetralones (417) and (419). Spin decoupling experiments confirmed that the 3-methyl derivative (417) was a 1:1 mixture of the enol and keto tautomers, (425) and (426). In the D_2O exchanged p.m.r. spectrum, C4-H of the enol (425) occurred as a broad singlet ($W_{\frac{1}{2}}$ 3Hz), whereas in the keto system (426) a doublet (J = 2Hz) was observed. This indicates that in (426), C4-H is

in the pseudoequatorial orientation. In the demethoxy derivative (390) the opposite orientation was found (δ 4.68, bs, $W_{\frac{1}{2}}$ 10Hz, C4-H). A similar result was obtained with the diester (419), obtained from dimethyl maleate (373). The p.m.r. spectra showed an approximately 3:2 ratio of the tautomers (427) and (428) with C4-H occurring as a broad singlet ($W_{\frac{1}{2}}$ 4.5Hz) and a doublet (J = 4.5Hz) respectively.

On treatment with acid, the tetralones (417) and (419) were converted to the respective naphthols (418) and (420).





(425) R = Me

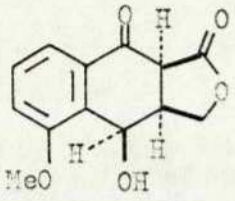
(427) R = CO_2Me

(426) R = Me

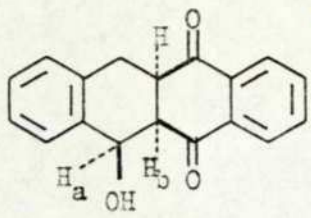
(428) R = CO_2Me

When the reaction was repeated with crotonolactone (379) as the Michael acceptor, the tetralone (421) was obtained as an amorphous solid m.p. 164-6°. The spectral data were consistent with the proposed structure. Analysis of the p.m.r. spectrum of (421) revealed that only one of the epimers had been isolated, and of note was the signal due to C4-H which occurred as a broad singlet at δ 5.40 and, on D_2O exchange, sharpened to a doublet of J = 3Hz. By virtue of the C3-H, C4-H vicinal coupling constant (J = 3Hz), the structure (429), with the cis-configuration, is proposed. In related systems the same coupling constant has been observed.

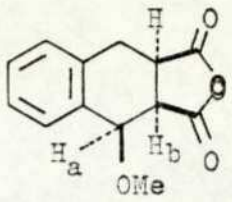
For example in the p.m.r. spectra of compounds (430) and (431), J_{Ha-H_b} = 3Hz[72]



(429)



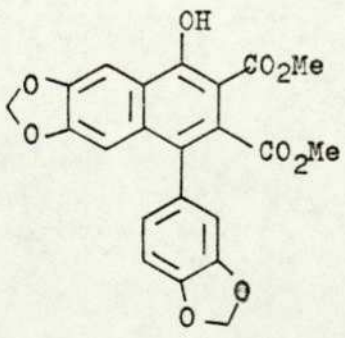
(430)



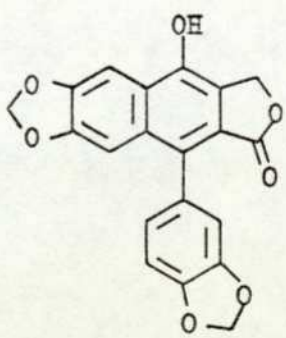
(431)

Brief treatment of the tetralone (429) with neat trifluoracetic acid afforded the naphthol lactone (422) (52%). After protection of the phenolic group this compound could be used for further aromatic ring homologation.

Several other naphthols are capable of transformation to naphthol lactones. Arnold[2] has reported that reduction of the diester (432) with sodium borohydride in methanol afforded taiwanin E (220) directly in 60% yield. In their studies on sorigenins, Horii et.al[73] prepared β-sorigenin



(432)

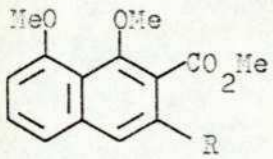


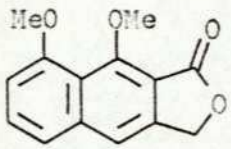
(220)

dimethyl ether (434) from the diester (433) by reduction of the corresponding anhydride.

The 3-methyl derivatives (369) and (418) are also latent lactones. For example Hauser and Rhee[41] found that reaction of the naphthoate (435) with NBS, followed by treatment of the resulting bromomethyl compound (436) with sodium hydroxide afforded the sorigenin derivative (434) in 85% yield.

Furthermore, the compounds (369) and (418), after suitable protection, might also undergo anion formation[43] and thus extend the synthetic use of these compounds considerably.





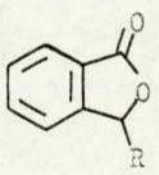
(433) R = CO_2Me

(435) R = Me

(436) R = CH_2Br

(434)

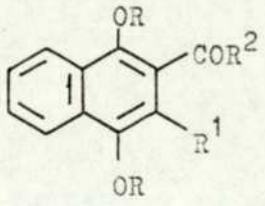
Since the completion of this work[74] there have been several reports of the reaction of phthalide anions in the preparation of 1,4-dihydroxy-naphthalenes.



(437) R = CN

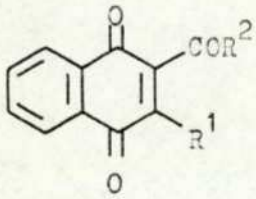
(438) R = SPh

(439) R = SO_2Ph

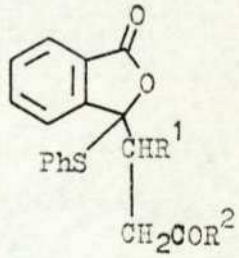


(440) R = H

(441) R = Me



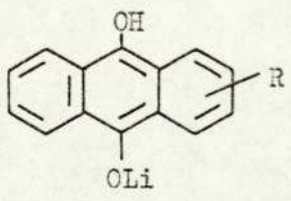
(442)



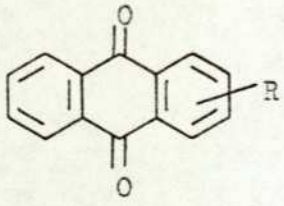
(443)

Reaction of the anion of 3-cyanophthalide (437) with various Michael acceptors[75], followed by oxidation of the resulting dihydroxy compound (440) afforded the quinones (442) in good yield. When the reaction was repeated with 3-thiophenylphthalide (438) only the Michael adducts (443) were isolated. Independent work by Hauser and Rhee[35] has shown that the sulphone derivative (439) does react with Michael acceptors to give, after methylation, the 1,4-dimethoxynaphthalenes (441). Interestingly both Krauss[75] and Hauser[35] report that the phthalides (437) and (439) react with α,β-unsaturated ketones and, furthermore, Hauser[35] found that the reaction proceeded with cyclohexenone. However attempts by both groups to isolate any of the intermediate tetralone systems were unsuccessful.

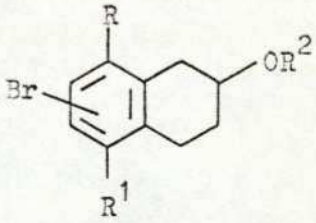
The use of phthalide anions for the preparation of substituted naphthols[74] has been extended to the preparation of substituted anthraquinones[76]. Reaction of phthalide anion with benzynes followed by air oxidation of the unstable anthrahydroquinone (444) gave the anthraquinones (445) in good yield.



(444)



(445)



(446)

This preparation of anthraquinones from phthalides would seem to offer a general reaction of wide scope. Since the addition of carbanions to arynes occurs regioselectively, the extension of the reaction to substituted bromobenzenes of the type (446) would provide a simple and very flexible synthesis of anthracyclinone synthons.

^{13}C n.m.r. spectra

The ^{13}C n.m.r. spectra for various naphthols synthesised in the course of the work described in this thesis are given below. The spectra were recorded on a Jeol FX 60 spectrometer using deuterochloroform as solvent. The chemical shifts are quoted in parts per million downfield from tetramethylsilane. The usual abbreviations are used in connection with n.m.r. data.

Spectral assignments were made with the aid of proton coupled spectra run in a 'gated' decoupling mode and also using additivity correlations.[77,78] The assignments of the majority of resonances are reasonably certain but where doubt occurs this is indicated in the tables by an asterisk.

Methyl 3,4-dimethyl-1-hydroxy-2-naphthoate (363)

Chemical Shift ppm	Multiplicity	Coupling Hz ^{1}J (CH), ^{3}J (CH)	Assignment	Calculated shift value
173.0	s		C=O	-
159.3	s		C-1	152.0
135.5	s		C-4a*	136.2
131.2	s		C-3*	135.5
129.4	dd	159.9, 8.6	C-6	128.1
127.1	s		C-4	126.2
124.5	d with further fine coupling	ca 163	C-5*, C-7*	122.9, 124.3
123.6	dd	158.7, 6.1	C-8*	122.5
123.1	s		C-8a	120.5
107.5	s		C-2	111.9
52.1	q	147.7	CO_2Me	-
19.5	q	128.2	Me	-
14.6	q	127.0	Me	-

Methyl 1-hydroxy-3-methyl-2-naphthoate (369)

Chemical Shift ppm	Multiplicity	Coupling Hz ^1J (CH), ^3J (CH)	Assignment	Calculated Shift value
173.2	s		C=O	-
162.7	s		C-1	153.7
136.2	s		C-4a*	136.0
135.0	s		C-3*	135.0
129.7	dd	158.7, 7.3	C-6	128.6
126.6	m		C-5*	127.0
125.0	m		C-7*	125.0
124.1	m		C-8*	122.2
120.7	d with further coupling	ca 160	C-4	119.6
106.3	s		C-2	112.5
52.2	q	147.7	CO_2Me	-
24.6	qd	129.4, 6.1	Me	-
			C-8a	121.6

2,3-Dicarbomethoxy-1-naphthol (372)

Chemical Shift ppm	Multiplicity	Coupling Hz ^{1}J (CH), ^{3}J (CH)	Assignment	Calculated Shift value
170.4	s		C=O	-
169.6	s		C=O	-
160.9	s		C-1	154.7
135.1	s		C-4a	135.1
130.2	dd	160.8, 8.5	C-6*	129.7
128.0	m		C-5*	129.0
127.3	m		C-7*	128.5
125.4	s		C-8a	125.5
124.0	dd	170.9, 6.1	C-4	123.9
119.7	dd	157.5, 4.9	C-8	122.7
103.0	s		C-2	110.0
52.8	q	147.7	CO_2Me	-
52.5	q	146.5	CO_2Me	-
			C-3	127.5

Methyl 3,4-dimethyl-1-hydroxy-5-methoxy-2-naphthoate (416)

Chemical Shift ppm	Multiplicity	Coupling Hz ^1J (CH), ^3J (CH)	Assignment	Calculated Shift value
172.8	s		C=O	-
157.9	s		C-1*	151.2
157.1	s		C-5*	150.2
131.5	s		C-3	134.6
128.2	s		C-4a	128.1
125.7	s		C-8a*	121.7
124.8	d	162.3	C-7	124.1
124.2	s		C-4*	120.1
116.6	dd	166.0, 7.3	C-8	114.6
109.9	dd	157.5, 7.3	C-6	105.8
108.4	s		C-2	112.2
55.6	q	144.0	O-Me	-
52.1	q	147.7	CO_2Me	-
19.6	q	128.1	Me	-
18.8	q	128.1	Me	-

Methyl 1-hydroxy-5-methoxy-3-methyl-2-naphthoate (418)

Chemical Shift ppm	Multiplicity	Coupling Hz ^{1}J (CH), ^{3}J (CH)	Assignment	Calculated Shift value
173.2	s		C=O	
162.0	s		C-5*	154.3
154.4	s		C-1*	153.0
134.4	s		C-3	134.1
127.9	s		C-4a	128.3
124.9	d	161.1	C-7	124.9
118.4	s		C-8a	122.8
115.9	dd	166.0, 7.3	C-8	114.3
114.6	dq	162.3, 6.1	C-4	113.5
107.6	dd	158.7, 8.5	C-6	106.3
106.8	s		C-2	112.8
55.6	q	144.0	-OMe	-
52.1	q	147.7	CO_2Me	-
24.7	qd	128.2, 6.1	Me	-

2,3-Dicarbomethoxy-5-methoxy-1-naphthol (420)

Chemical Shift ppm	Multiplicity	Coupling Hz ^1J (CH), ^3J (CH)	Assignment	Calculated Shift value
170.7	s		C=O	-
170.2	s		C=O	-
160.7	s		C-5*	156.3
155.9	s		C-1*	154.0
129.3	s		C-4a*	127.4
127.9	d	162.4	C-7	128.3
127.2	s		C-8a*	126.7
126.7	s		C-3*	126.6
116.0	dd	166.0, 6.1	C-8	114.8
114.5	d	167.2	C-4	117.8
108.6	dd	158.7, 8.5	C-6	107.4
103.9	s		C-2	110.3
55.7	q	144.0	O-Me	-
52.9	q	147.7	CO_2Me	-
52.6	q	147.7	CO_2Me	-

EXPERIMENTAL

SECTION

All melting points were determined on a Kofler hot-stage apparatus and are uncorrected.

Infra-red (I.R.) spectra were recorded on a Perkin Elmer 157G spectrometer. Samples were prepared as chloroform solutions unless otherwise stated.

Ultra-violet (U.V.) spectra were recorded for ethanolic solutions in silica cells with a Pye-Unicam SP 800 instrument.

Proton nuclear magnetic resonance (p.m.r.) spectra were recorded on a Jeol MH 100 spectrometer. Generally deuteriochloroform was used as solvent with tetramethylsilane (TMS) as internal reference. Coupling constants are quoted as J values in Hz. The abbreviations s = singlet, d = doublet, dd = doublet doublet, t = triplet, q = quartet, m = complex multiplet, b = broadened, exch. = disappears on addition of D_2O, are used in connection with p.m.r. data.

Mass spectra were recorded by the Physical and Chemical Measurements Unit (P.C.M.U.), Harwell.

Thin layer chromatography (t.l.c.) was carried out on Kieselgel GF_{254} (Merck) grade silica gel. Chromatograms were monitored by viewing under u.v. light and developed in iodine vapour. Preparative t.l.c. was carried out on plates of 1mm thickness, under similar conditions. Large scale separations were carried out using columns packed with MFC 60-120 mesh silica, with a silica to compound weight ratio of 50:1.

Solvent mixtures are described in ratios of volumes. Tetrahydrofuran (THF) was dried over and distilled from lithium aluminium hydride under an atmosphere of argon immediately before use. Ether

and benzene were dried over sodium. Acetone ('Analar' grade) and dichloromethane were stored over 4Å molecular sieves 'Petroleum' refers to the fraction of b.pt. 60–80°. Extracts were dried over anhydrous sodium sulphate and were evaporated under reduced pressure on a Buchi rotary evaporator.

o-Acetylphenyl ethyl carbonate (250a)

A solution of o-hydroxyacetophone (249) (2.4ml, 0.02 mole) in pyridine (4 ml) at 0-5° was treated dropwise with ethyl chloroformate (3.7ml, 0.04 mole). After ½ hour the mixture was poured into 1N hydrochloric acid solution (120 ml) containing ice (40 g), extracted with ether (3 x 50 ml) and dried. The organic phase was then evaporated to give the carbonate (250a) (4.1 g, 96%) as a yellow oil. ν_{max} (neat) 1770, 1695cm^{-1}, δ 1.37 (3H, t, J = 7 Hz), 2.57 (3H, s) 4.33 (2H, q, J = 7 Hz), 7.10 - 7.97 (4H, m).

Attempted preparation of ethyl salicoylacetate (251a)

A mixture of the carbonate (250a) (80 mg, 0.8 mmol) and sodium (18 mg, 0.8 mmol) in dry ethylformate (0.8 ml) was stirred for 16 hours. The resulting orange-brown solution was then poured into a vigorously-stirred mixture of ice (3g) and 2N hydrochloric acid solution (10 ml) and extracted with ether (3 x 10 ml). The organic phase was washed with water (2 x 10 ml), dried and evaporated to give a brown oil. P.m.r. and t.l.c. analysis of this material showed that the ester (251a) was not present and that the majority of the material was very polar.

Ethyl salicoylacetate (251a)

To a stirred suspension of sodium hydride (1.44 g, 0.06 mole) and diethyl carbonate (4.72 g, 0.04 mole) in refluxing dry ether (30 ml) was added a solution of o-hydroxyacetophenone (249) (2.36 g, 0.02 mole) in dry ether (30 ml) over a period of 3 hours. After 16 hours glacial acetic acid (10 ml) and then water (30 ml) were added to the reaction mixture. The solution was extracted with ether (4 x 75 ml), the extracts were neutralised with sodium bicarbonate solution, dried and evaporated. The resulting brown oil was distilled under reduced pressure to give the keto-ester (251a) (3.23 g, 78%) b.p. 170° (0.5 mm) υ_{max} 3100, 1730, 1635cm^{-1}, δ 1.27 (3H, t, J = 7 Hz), 4.01 (2H, s), 4.23 (2H, q, J = 7 Hz), 6.72 - 7.84 (4H, m), 12.07 (1H, s, exch). (lit.[12] δ 1.2 (3H, t) 3.99 (2H, s), 4.22 (2H, q), 6.7 - 7.8 (4H, m), 11.8 (1H, s))

2-Carboethoxy-3-methylchromone (246a)

The ester (251a) (100 mg, 0.48 mmol), sodium acetate (100 mg, 1.22 mmol) and acetic anhydride (0.4 ml) were stirred at 110° to disappearance of starting material (t.l.c.). The mixture cooled, water (3 ml) added and a yellow solid separated. The mixture was extracted with ether (3 x 20 ml), the extracts washed with saturated sodium bicarbonate solution (10 ml), 10% sodium hydroxide solution (10 ml) and water (10 ml). The dried organic phase was evaporated to afford

a yellow solid. Crystallisation from petroleum afforded the chromone (246a) (70 mg, 63%) m.p. 67-9° (from petroleum) λ_{max} (ε) 300 n.m. (6420), 289 (6530), 228 (17970), ν_{max} (nujol mull) 1725, 1630, 1575cm^{-1}, δ 1.40 (3H, t, J = 7 Hz), 2.51 (3H, s), 4.42 (2H, q, J = 7 Hz), 7.19-7.79 (3H, m), 8.05 - 8.28 (1H, m). (Found: C, 67.08; H, 5.26%. $C_{13}H_{12}O_4$ requires C, 67.23; H, 5.21%).

Attempted benzoxanthenone synthesis with 3-carboethoxy-2-methylchromone (246a) and bromobenzene.

To a stirred solution of diisopropylamine (131 mg, 1.3 mmol) in THF (ml) under nitrogen at -5 to 10° was added a solution of n-butyl lithium (1.6M, 0.81 ml, 1.3 mmol) in hexane. After 15 minutes a solution of the chromone (246a) (278 mg, 1.2 mmol) in THF (1 ml) was added, followed, after 1 hour, by sodamide (83 mg, 2.1 mmol), and sodium t-butoxide (77 mg, 0.8 mmol). The solution was immediately cooled to -70° and treated with a solution of bromobenzene (63 mg, 0.4 mmol) in THF (1 ml). After 30 minutes, the mixture was warmed to room temperature and stirring was continued for 16 hours. The mixture was then poured into water (7 ml), acidified with 2N hydrochloric acid solution (5 ml) and extracted with ether (3 x 20 ml). The extract dried and evaporated to give a brown viscous oil (300 mg). P.m.r. and t.l.c. analysis of the crude reaction mixture indicated that the benzoxanthenone (248) was not present. Preparative t.l.c. (chloroform, 2 elutions) gave 10 fractions from which small ($<$15 mg) amounts of material could be recovered. The majority of material was of base-line origin. Apart

from the chromone (246a), no discrete compounds were observed in the fractions.

Stability of the chromone (246a) to bases

a) Lithium diisopropylamide (LDA):- To a stirred solution of diisopropylamine (13 mg, 0.13 mmol) in THF (1 ml) under nitrogen at -5 to -10° was added a solution n-butyl lithium (1.6M, 0.08 ml, 0.13 mmol) in hexane. After 15 minutes a solution of the chromone (246a) (28 mg, 0.12 mmol) in THF (1 ml) was added. The solution was cooled to -70° and allowed to reach room temperature over 16 hours. The mixture was then added to water (5 ml), acidified with 2N hydrochloric acid solution (2 ml) and extracted with ether (3 x 4 ml). The extracts were dried and evaporated to give an orange-brown viscous oil. T.l.c. of the mixture was similar to that of the previous reaction.

b) Sodamide:- To a stirred suspension of sodamide (16 mg, 0.4 mmol) in THF (1 ml) under nitrogen at -5° was added solution of the chromone (246a) (12 mg, 0.05 mmol) in THF (1 ml). After 16 hours the mixture was worked up as in (a) to afford an orange oil. Tlc of the mixture showed the presence of (246a) and some polar material. Comparison with the previous reaction shows that (246a) is more stable to sodamide than LDA.

c) Sodium hydride:- To a suspension of sodium hydride (40 mg of 60% dispersion in oil, 0.1 mmol) in THF (1 ml) under nitrogen at -5° was added a solution of the chromone (246a) (11.6 mg, 0.05 mmol) in THF (1 ml). After 16 hours the mixture was worked up as in (a) to give an orange gum. Tlc showed a small amount of starting material but the majority was very polar.

Attempted benzoxanthanenone synthesis with the chromone (246a) and 2,5-dimethoxybromobenzene (226)

To a stirred syspension of sodamide (418 mg, 11 mmol) in THF (5 ml) under nitrogen was added a solution of the chromone (246a) (720 mg, 3.1 mmol) in THF (3 ml). After 1 hour a solution of 2,5-dimethoxybromobenzene (226) (180 mg, 0.88 mmol) in THF (5 ml) was added and the mixture stirred for 24 hours. The mixture was then added to water (20 ml), acidified with 2NHCl (10 ml) and extracted with ether (3 x 40 ml). The dried organic phase was evaporated to afford a brown gum. Chromatography (dichloromethane, then 1% methanol-dichloromethane) gave the starting materials (226) (35 mg),(246a) (39 mg). Very small amounts of other non-polar materials were isolated but the majority of the reaction mixture was brown polar material. In the p.m.r. spectra of the fractions examined, no aromatic methoxy protons were detected.

2-Methyl-3-acetylchromone (258a) was prepared by the method of Wittig[81]

2- Methyl-3-benzoylchromone (258b):- was prepared by the method of Müller[77] from 2-benzoylacetophenol[80].

Attempted benzoxanthenone synthesis with:-

2-Methyl-3-acetylchromone (258a) To a stirred suspension of sodamide (78 mg, 2 mmol) in THF (5 ml) under nitrogen at -5 to -10° was added a solution of the chromone (258a) (101 mg, 0.5 mmol) in THF (1 ml). After 1 hour the mixture was cooled to -70° and a solution of bromobenzene (40 mg, 0.25 mmol) in THF (1 ml) was added. The reaction was allowed to warm to room temperature overnight (16 hours). The mixture was then poured into water (5 ml), acidified with 2N hydrochloric acid solution, extracted with ether (3 x 15 ml), dried and evaporated. Preparative t.l.c. (dichloromethane) of the brown residue afforded a small amount of the chromone (258a) and mainly polar material that gave an indistinct p.m.r. spectrum. No cyclized material could be detected.

2-Methyl-3-benzoylchromone (258b) The reaction was repeated with the chromone (258b) (132 mg, 0.5 mmol). Preparative t.l.c. of the crude reaction mixture afforded mainly polar material, a small amount of the chromone (258b) and two fluorescent, non-polar fractions (ca6 mg). The U.V. spectra of both fractions showed that the benzoxanthenone (259b) (λ_{max} (log ε) 238n.m. (4.39), 262 (4.83), 311 (3.81), 3.23 (3086, 390 (3.63)[14]) was not present.

Ethyl 2-methylbenzoate

2-Methylbenzoic acid (60 g, 0.45 mole) was dissolved in ethanol (400 ml) to which acetyl chloride (20 ml) had been added to produce an approximately 3% solution of HCl. The solution was brought to reflux for 12-13 hours after which only traces of the starting material were detectable (t.l.c.). Evaporation and distillation at reduced pressure gave ethyl 2-methylbenzoate (63 g, 84%) b.p. 100° (10 mm) (Lit.[67] 102° (13 mm) ν_{max} (film) 1715cm^{-1}.

2-Methylbenzyl alcohol

Ethyl 2-methylbenzoate (35 g, 0.21 mmol) was dissolved in dry ether (250 ml) and was added slowly with stirring to a suspension of lithium aluminium hydride (10 g) in dry ether (250 ml) under an atmosphere of nitrogen at 0°C. The mixture was stirred at 0-5° for 1-2 hours until work-up of a small aliquot revealed that no ester remained. Saturated ammonium chloride solution (200 ml) was then cautiously added, at 0°, ensuring that adequate stirring was maintained. The reaction mixture was stirred for a further hour before separating the phases and extracting the aqueous phase with more ether, washing the combined organic extracts with water and drying. Evaporation of the solvent afforded 2-methylbenzyl alcohol (25 g, 90%) as a crystalline solid. ν_{max} (nujol mull) 3400 cm^{-1}.

2-Methylbenzaldehyde (213)[2]

2-Methylbenzyl alcohol (25 g, 0.20 mole) and active manganese dioxide (100 g) in dichloromethane (500 ml) were stirred under nitrogen until no starting material could be detected (t.l.c.). The mixture was filtered through celite washing well with more solvent and the filterate was evaporated to yield 2-methylbenzaldehyde (213) (24 g, 90%) as a pale yellow oil. ν_{max} (film) 2750, 1690cm^{-1}, δ 2.6 (3H,s), 6.9 - 7.7 (4H, m), 10.16 (1H, s).

2-Methylbenzaldehyde (213) was not purified by distillation as considerable losses were usually incurred due to the volatility of the material and its susceptibility to oxidation. Instead the material was dissolved in ether and was shaken with an equal volume of saturated sodium metabisulphite solution at room temperature for 3 hours, whereupon white crystals of the bisulphite complex were deposited. The complex was filtered off and washed with ether before drying in vacuo. 2-Methylbenzaldehyde was routinely stored as its bisulphite complex, being readily released immediately prior to use by the following procedure:-

A weighed quantity of the bisulphite complex was dissolved in a little water and excess solid sodium carbonate was added. The solution was directly extracted with dichloromethane and the organic phase was washed once with water before drying, in a flask shielded from light, and evaporation of the solvent to afford pure aldehyde (213) (100%).

Methyl 2-methylbenzoate (277)

2-Methylbenzoic acid (20 g, 0.15 mole) was refluxed in a large excess of methanol (50 g, 1.56 mole) in the presence of a trace of concentrated sulphuric acid (2 ml) for 24 hours. The reaction was cooled, water (50 ml) added and the mixture extracted with ether (3 x 75 ml). The extracts were washed with saturated sodium bicarbonate solution (3 x 25 ml), dried and evaporated. Distillation of the residue at reduced pressure gave the ester (277) (18.5 g, 84%) b.p. 95-6° (14 mm) (Lit.[67] 97° (15 mm)).

Attempted anthrone synthesis with methyl 2-methylbenzoate (277) and bromobenzene

To a stirred solution of diisopropylamine (369 mg, 3.65 mmol) in THF (10 ml) under nitrogen at -5 to -10° was slowly added a solution of n-butyl lithium (2.1M, 1.73 ml, 3.65 mmol) in hexane. After 15 minutes a solution of methyl 2-methylbenzoate (277) (500 mg, 3.33 mmol) in THF (3 ml) was added. After 10 minutes the red solution was treated with sodamide (252 mg, 6.5 mmol) and sodium t-butoxide (227 mg, 2.6 mmol). The mixture was cooled to -70° and treated with a solution of bromobenzene (174 mg, 1.1 mmol) in THF (1 ml). After 30 minutes at -70° the mixture was allowed to reach room temperature over 21 hours. The mixture was then poured into 2N hydrochloric acid solution (20 ml), extracted with dichloromethane (3 x 15 ml), dried and evaporated. Trituration of the orange residue with dichloromethane-petroleum afforded 2-methylbenzamide (281) (9 mg) m.p. 138-140 (from dichloromethane)

(lit[67] 138°). (Found: M^+ 135.0675, C_8H_9NO requires M 135.0684).

Preparative t.l.c. (chloroform-petroleum, 1:1) of the residue gave many non-polar fractions (< 4 mg). In none of the fractions examined could any anthrone (280) or anthrol (279) be detected.

The reaction was repeated with HMPA as co-solvent and again no cyclised material was detected.

Attempted anthracene synthesis with o-tolualdehyde (213) and bromobenzene

a) To a stirred solution of diisopropylamine (465 ml, 4.6 mmol) in THF (10 ml) at -5 to -10° under nitrogen was added a solution of n-butyl lithium (2.1M, 2.2 ml, 4.6 mmol) in hexane. After 15 minutes a solution of the aldehyde (213) (500 mg, 4.2 mmol) in THF (3 ml) was added, followed, after 1½ hours, by sodamide (312 mg, 8 mmol), and sodium t-butoxide (280 mg, 3.2 mmol). The mixture was then cooled to -70° and treated with a solution of bromobenzene (219 mg, 1.4 mmol) in THF (1 ml). After 30 minutes at -70°, the mixture was slowly allowed to reach room temperature by stirring over 21 hours. The mixture was then added to 2N hydrochloric acid solution (25 ml), extracted with dichloromethane (3 x 20 ml), dried and evaporated. Preparative t.l.c. (chloroform-petroleum, 2:3) of the brown residue afford an impure sample of anthracene (278) (ca 4 mg, ca 1%), identified by comparison of the U.V. spectrum and t.l.c. with authentic material.

The reaction was repeated with HMPA (4 ml) as co-solvent. Preparative t.l.c. of the residue gave impure anthracene (278) (ca 10 mg, ca 4%).

b) To a stirred solution of tetramethylpiperidine (1.68 ml, 10 mmol) in THF (5 ml) under argon at -40° was slowly added a solution of n-butyl lithium (2.0M, 5 ml, 10 mmol) in hexane. After 15 minutes a solution of o-tolualdehyde (213) (360 mg, 3 mmol) in THF (3 ml) was added. After 1 hour the red/black mixture was cooled to -70° and treated with a solution of bromobenzene (314 mg, 2 mmol) in THF (1 ml) and the mixture allowed to reach room temperature over 18 hours. The mixture was then poured into ether (50 ml), washed with 2N hydrochloric acid solution (2 x 15 ml), water (2 x 20 ml), dried and evaporated. T.l.c. and p.m.r. analysis of the resulting brown oil revealed that no anthracene (278) was present. Traces of the aldehyde (213) remained.

c) To a stirred solution of tetramethyl piperidine (1.2 ml, 7 mmol) in dry benzene (30 ml) under argon at 25° was added a solution of n-butyl lithium (2.0M, 3.5 ml, 7 mmol) in hexane. After 10 minutes a solution of o-tolualdehyde (213) (120 mg, 1 mmol) in benzene (5 ml) was added. After 30 minutes the red solution was treated with a solution of bromobenzene (157 mg, 1 mmol) in benzene (2 ml). The mixture was refluxed for 30 minutes, then poured into ether (50 ml), washed with 2N hydrochloric acid solution (2 x 15 ml), water (2 x 10 ml), dried and evaporated. Preparative t.l.c.(chloroform-petroleum, 3:7) of the residue afforded the anthracene (278) (3 mg) and the aldehyde (213) (30 mg).

The reaction was repeated using HMPA (15 ml) as co-solvent. This gave anthracene (278) (4 mg) and the aldehyde (213) (18 mg).

Attempted alkylation of o-tolualdehyde (213)

a) To a stirred solution of n-butyl lithium (2.0M, 1.5 ml, 3 mmol) in hexane in dry ether (5 ml) under argon at -40° was added a solution of o-tolualdehyde (213) (240 mg, 2 mmol) in ether (5 ml). After 1 hour, the yellow mixture was warmed to room temperature and methyl iodide (0.31 ml, 5 mmol) added. After 15 minutes, the light yellow mixture was poured into dichloromethane (40 ml) and washed with 2N hydrochloric acid solution (3 x 10 ml). The organic phase was dried and evaporated to give a light yellow oil. P.m.r. analysis of the crude reaction mixture showed that the starting aldehyde (213) had been consumed but no material containing an ethyl group was present.

b) The reaction was repeated with HMPA as solvent. After 5 mins, methyl iodide (0.31 ml, 5 mmol) was added to the orange reaction mixture. An immediate loss of colour was observed. The mixture was worked-up as described in (a) to give a yellow oil. P.m.r. analysis of the crude reaction mixture showed only traces of the starting aldehyde (213) and that no material containing an ethyl group was present.

c) To a solution of tetramethylpiperidine (0.164 ml, 1 mmol) in HMPA (10 ml) and benzene (10 ml) under argon at -20° was added a solution of n-butyl lithium (2.0M, 0.5 ml, 1 mmol) in hexane. After 15 minutes the solution was warmed to room temperature and a solution of o-tolualdehyde (213) (120 mg, 1 mmol) in benzene (1 ml) was added. After 1 hour, methyl iodide (0.37 ml, 6 mmol) was added and the mixture stirred for a further 15 minutes. Work-up as in (a) afforded material which contained no starting aldehyde (213) and no material containing an ethyl group.

Benzocyclobutenyl acetate[3]

To anthranilic acid (25 g, 0.18 mole) and trichloroacetic acid (0.29 g) in THF (180 ml), cooled in ice-water, was added, with stirring, amyl nitrite (26.3 g, 0.23 mole) over one minute. The mixture was then allowed to reach room temperature over 2 hours. The solid was collected on a Buchner funnel under low vacuum to prevent dryness, washed with ice-cold THF until the washings were colourless, and then with ice-cold dichloromethane (100 ml). The solid was then slurried with dichloromethane and stored at 0°. The slurry was then added in small portions over 1 hour to a mixture of vinyl acetate (100 g, 1.16 mole) and dichloromethane (100 ml) which was gently refluxing with stirring in a wide-necked flask. The mixture was then left for 1½ hours. The solvents were removed under reduced pressure and the residue was steam distilled, collecting about 400 ml of distillate. The distillate was extracted

with ether (4 x 100 ml), dried and evaporated to give the crude ester (38% based on anthranilic acid), pure enought for general use. A pure sample could be obtained by removing the main contaminate, biphenylene, by passing the mixture through a column of silica gel, eluting the biphenylene with petroleum and benzocyclobutenyl acetate with chloroform. δ 2.10 (3H, s), 3.20 (1H, dd, J = 2, 14 Hz), 3.72 (1H, dd, J = 5, 14 Hz), 5.93 (1H, dd, J = 2, 5 Hz), 7.3 (4H, bs).

Benzocyclobutenol (221)[3,26]

Benzocyclobutenyl acetate (crude material, 3.25 g, 0.02 mmol) in dry methanol (150 ml) was refluxed for 3 hours with Amberlite 1R 120H ester exchange resin (20 g, washed well with methanol). The mixture was filtered and the filtrate evaporated and cooled. The resulting solid was recrystallised from petroleum to afford the alcohol (221) (1.56 g, 65%) m.p. 58-9° (needles from petroleum) (lit[26] 58-9°). δ 3.17 (1H, bs, exch), 3.22 (1H, dd, J = 2, 15 Hz), 3.60 (1H, dd, J = 5, 15 Hz), 5.22 (1H, dd, 2, 5 Hz), 7.2 (4H, bs).

1-Methoxyanthracene (292)

a) To a stirred solution of tetramethylpiperidine (0.51 ml, 3 mmol) in THF (25 ml) at -45° under argon was slowly added a solution of n-butyl lithium (1.8M, 1.67 ml, 3 mmol). After 15 minutes the solution was warmed to room temperature and a solution of benzocyclobutenol (221) (120 mg, 1 mmol) and o-bromoanisole (291) (187 mg, 1 mmol) in THF (10 ml) was added dropwise over 40 minutes. After 1 hour the black mixture

was poured into 2N hydrochloric acid solution (30 ml), extracted with ether (3 x 75 ml) and the extract dried and evaporated. Preparative t.l.c., chloroform/petroleum, 1:4, 2 elutions) afforded a light green oil (65 mg) as a fluorescent non-polar band. The n.m.r. spectrum of the oil showed the material to be a 3:1 mixture of 1-methoxyanthracene (292) and the starting o-bromoanisole (291). Integration of the signals due to the methoxy group revealed that the yield of the anthracene (292) was 24% and that 8% of (291) had been recovered. Attempts to separate the mixture proved unsuccessful.

b) To a stirred solution of tetramethylpiperidine (0.37 ml, 2.2 mmol) in THF (25 ml) under argon at -50° was slowly added a solution of n-butyl lithium (1.68M, 1.22 ml, 2.2 mmol) in hexane. After 20 minutes the solution was warmed to -30° and a solution of benzocyclobutenol (221) (120 mg, 1 mmol) and o-bromoanisole (187 mg, 1 mmol) in THF (15 ml) added dropwise over 105 minutes. After 4 hours the reaction mixture was worked-up as in example (a). Chromatography gave only o-bromoanisole (291) (120 mg).

c) To a stirred solution of tetramethylpiperidine (0.25 ml, 1.5 mmol) in THF (20 ml) under argon at -50° was slowly added a solution of n-butyllithium (2.5M, 0.6 ml, 1.5 mmol) in hexane. After 15 minutes the mixture was warmed to 0° and a solution of benzocyclobutenol (221) (60 mg, 0.5 mmol) and o-bromoanisole (291) (94 mg, 0.5 mmol) in THF (10 ml) added dropwise over 60 minutes. After ½ hour at 0° the reaction mixture was warmed to room temperature and worked-up as in example (a). Chromatography gave a 1:4 mixture (61 mg) of (292) (12%) and (291) (50%).

d) To a stirred solution of tetramethylpiperidine (0.25 ml, 1.5 mmol) in THF (6 ml) at -50° under argon was slowly added a solution of n-butyl lithium (2.5M, 0.6 ml, 1.5 mmol) in hexane. After 15 minutes the mixture was warmed to room temperature and a solution of benzocyclobutenol (221) (60 mg, 0.5 mmol) and o-bromoanisole (291) (94 mg, 0.5 mmol) in THF (2 ml) was quickly added (< 1 minute). After 40 minutes the black reaction mixture was worked-up as in example (a). Chromatography gave a 6:1 mixture (42 mg) of (292) (35%) and (291) (5%).

e) To a stirred solution of tetramethylpiperidine (0.67 ml, 4 mmol) in THF (20 ml) under argon at -50° was slowly added a solution of n-butyl lithium (2.5M, 1.6 ml, 4 mmol) in hexane. After 30 minutes the mixture warmed to room temperature and a solution of benzocyclobutenol (221) (360 mg, 3 mmol) and o-bromoanisole (291) (94 mg, 0.5 mmol) in THF (2 ml) was quickly added. After 45 minutes, the mixture was worked-up as in example (a). Chromatography gave a 1:1.3 mixture (34 mg) of (292) (15%) and (291) (20%).

f) To a stirred solution of tetramethylpiperidine (0.34 ml, 2 mmol) in THF (7 ml) under argon at -50° was slowly added a solution of n-butyl lithium (2.5M, 0.8 ml, 2 mmol) in hexane. After 20 minutes was warmed to room temperature and a solution of benzocyclobutenol (221) (120 mg, 1 mmol) and o-bromoanisole (291) (94 mg, 0.5 mmol) in THF (2 ml) was quickly added. After 45 minutes the black reaction mixture was poured into 2N hydrochloric acid solution (20 ml), extracted with ether (3 x 50 ml) and the extracts dried and evaporated. Preparative t.l.c. (chloroform/petroleum, 1:4, 2 elutions) gave 1-methoxyanthracene (292)

(32 mg, 31%) as a light green non-polar band. The product was recrystallised from methanol to afford light green needles m.p. 69.5-71°. (lit[82]. 70°). δ 4.08 (3H, s), 6.72 - 6.80 (1H, m), 7.20 - 7.66 (4H, m), 7.92 - 8.16 (2H, m), 8.40 (1H, s), 8.88 (1H, s).

2-Methylanthracene (298)

To a stirred solution of tetramethylpiperidine (0,34 ml, 2 mmol) in THF (6 ml) at -60° under argon was slowly added a solution of n-butyl lithium (2.5M, 0.8 ml, 2 mmol) in hexane. After 25 minutes the solution was brought to room temperature and a solution of benzocyclobutenol (221) (120 mg, 1 mmol) and p-bromotoluene (297) (86 mg, 0.5 mmol) in THF (2 ml) was added. The reaction mixture immediately went black. After 40 minutes the reaction mixture was poured into 2N hydrochloric acid solution (20 ml), extracted with ether (3 x 20 ml), dried and evaporated. Preparative t.l.c. (dichloromethane/petroleum, 1:9) of the residue afforded 2-methylanthracene (298) (24 mg, 25%) m.p. 195-6° (from dichloromethane-petroleum) (Lit[67], 199°), δ 2.58 (3H, s), 7.32 - 8.18 (7H, m), 8.42 (1H, s), 8.50 (1H, s).

Using m-bromotoluene (299) The above conditions were reproduced using m-bromotoluene (299) (86 mg, 0.5 mmol). Chromatography gave 2-methylanthracene (298) (18 mg, 19%) identicle in all respects to the product obtained previously using p-bromotoluene (297).

1-Methylanthracene (296)

To a stirred solution of tetramethylpiperidine (0.34 ml, 2 mmol) in THF (6 ml) at -60° under argon was slowly added a solution of n-butyl lithium (2.5M, 0.8 ml, 2 mmol) in hexane. After 25 minutes the solution was brought to room temperature and a solution of benzocyclobutenol (221) (120 mg, 1 mmol) and o-bromotoluene (295) (86 mg, 0.5 mmol) in THF (2 ml) was quickly added. The reaction mixture immediately went black. After 40 minutes the reaction mixture was poured into 2N hydrochloric acid solution (20 ml), extracted with ether (3 x 20 ml), dried and evaporated. Preparative t.l.c. (petroleum, 2 elutions) of the residue afforded 1-methylanthracene (296) (14 mg, 15%) m.p. 84-5° (from methanol) (lit[67] 85-6°) δ 2.85 (3H, s), 7.31 - 8.25 (7H, m), 8.54 (1H, s), 8.66 (1H, s).

Anthracene (278)

To a stirred solution of tetramethylpiperidine (0.34 ml, 2 mmol) in THF (6 ml) at -60° under argon was slowly added a solution of n-butyl lithium (2.5M, 0.8 ml, 2 mmol) in hexane. After 25 minutes the solution was brought to room temperature and a solution of benzocyclobutenol (221) (120 mg, 1 mmol) and bromobenzene (293) (78.5 mg, 0.5 mmol) in THF (2 ml) was quickly added. The reaction mixture immediately went black. After 40 minutes the mixture was poured into 2N hydrochloric acid solution (20 ml), extracted with ether (3 x 20 ml), dried and evaporated. Preparative t.l.c. (chloroform/petroleum, 1:4, 2 elutions) of the residue afforded anthracene (278) (18 mg, 20%) m.p. 214 - 6°

(from chloroform/methanol) (lit[67] 216°) δ 7.28 - 7.48 (4H, m), 7.80 - 8.00 (4H, m), 8.32 (2H, s).

The reaction was repeated with chlorobenzene (294) (67 mg, 0.5 mmol) as the benzyne precursor. Chromatography gave anthracene (278) (11 mg, 12%) identicle with previously obtained material.

Attempted preparation of 1,4-dimethoxyanthrancene

To a stirred solution of tetramethylpiperidine (0.34 ml, 2 mmol) in THF (6 ml) at -60° under argon was slowly added a solution of n-butyl lithium (2.5M, 0.8 ml, 2 mmol) in hexane. After 25 minutes the solution was brought to room temperature and a solution of benzocyclobutenol (221) (120 mg, 1 mmol) and 2,5-dimethoxybromobenzene (226) (109 mg, 0.5 mmol) in THF (2 ml) was quickly added. After 40 minutes the mixture was poured into 2N hydrochloric acid solution (20 ml), extracted with ether (3 x 20 ml), dried and evaporated. Preparative t.l.c. (chloroform/petroleum, 2:3 and then 1:1) of the residue afforded a gum (8 mg) as a fluorescent non-polar band. The p.m.r. spectrum of this material showed several -OMe resonances at ~δ 4.0 but in the absence of any resonances due to the C9, 10 protons, the presence of 1,4-dimethoxyanthracene could not be confirmed.

Reaction of o-tolualdehyde (213) and o-bromoanisole (291) with lithium tetramethylpiperidine

To a stirred solution of tetramethylpiperidine (0.34 ml, 2 mmol) in THF (6 ml) at -60° under argon was slowly added a solution of n-butyl lithium (2.5M, 0.8 ml, 2 mmol) in hexane. After 25 minutes the mixture was brought to room temperature and a solution of o-tolualdehyde (213) (120 mg, 1 mmol) and o-bromoanisole (291) (94 mg, 0.5 mmol) in THF (1 ml) was quickly added. This produced a black solution. After 40 minutes the mixture was poured into dichloromethane (30 ml), washed with 2N hydrochloric acid solution (2 x 10 ml), water (10 ml) dried and evaporated. T.l.c. and p.m.r. analysis of the resulting brown gum showed that no 1-methoxyanthracene (292) was present. The starting aldehyde and only traces of the bromide were observed.

Reaction of benzocyclobutenol (221) and o-bromoanisole (291) with sodamide

To a stirred suspension of sodamide (from sodium, 92 mg, 4 mmol) in THF (15 ml) under argon at room temperature was added a mixture of benzocyclobutenol (221) (120 mg, 1 mmol) and o-bromoanisole (291)(187 mg, 1 mmol). After 14 hours the mixture was poured into 2N hydrochloric acid solution (10 ml), extracted with dichloromethane (3 x 20 ml), dried and evaporated. T.l.c. and p.m.r. analysis of the residue showed that none of the anthracene (292) had formed, that the alcohol (221) had been consumed and that a large amount of the bromide (291) was still present.

Attempted anthrone synthesis with o-tolunitrile (302) and o-bromoanisole (291)

a) To a stirred solution of sodamide (from sodium, 4.5 mmol) in liquid ammonia (30 ml) was added a solution of o-tolunitrile (302) (117 mg, 1 mmol) in dry ether (1 ml). A grape-red solution was immediately obtained and after 15 minutes a solution of o-bromoanisole (291) (374 mg, 2 mmol) in dry ether (1 ml) was added. After 1½ hours ammonium chloride (0.6 g) was added and the ammonia evaporated. The reaction mixture was dissolved in water (20 ml) and extracted with ether (3 x 15 ml). The organic phase was washed with 2N hydrochloric acid solution (5 ml) dried and evaporated. Preparative t.l.c. (chloroform/petroleum, 1:4, 3 elutions) afforded the bromide (291) (73 mg), o-tolunitrile (302) (40 mg) and the nitrile (306) (27 mg, ca 15%), slightly contaminated, whose p.m.r. spectrum showed resonces inter alia at δ 3.72 (3H, s), 4.10 (2H, s).

b) To a stirred solution of tetramethylpiperidine (0.34 ml, 2 mmol) in THF (5 ml) at -40° under argon was slowly added a solution of n-butyl lithium (2.5M, 0.8 ml, 2 mmol) in hexane. After 15 minutes the mixture was warmed to room temperature and a solution of o-tolunitrile (302) (117 mg, 1 mmol) and o-bromoanisole (291) (94 mg, 0.5 mmol) in THF (2 ml) was quickly added. The reaction mixture immediately became red in colour. After 1 hour the mixture was poured into dichloromethane (50 ml), washed with 2NHCl (2 x 10 ml), water (2 x 10 ml) dried and evaporated. T.l.c. and p.m.r. analysis of resulting residue revealed that the starting materials (302) and (291) were present. No phenylated

or cyclised material could be detected.

c) To a stirred solution of tetramethylpiperidine (0.34 ml, 2 mmol) in THF (5 ml) under argon at -40° was slowly added a solution of n-butyl lithium (2.5M, 0.8 ml, 2 mmol) in hexane. After 15 minutes a solution of o-tolunitrile (302) (117 mg, 1 mmol) in THF (1 ml) was added and, after 5 minutes, the red solution was treated with a solution of o-bromoanisole (291) (94 mg, 0.5 mmol). After warming to room temperature over 3 hours the mixture was poured into dichloromethane (50 ml), washed with 2N hydrochloric acid solution (2 x 10 ml), water (2 x 10 ml), dried and evaporated. Preparative t.l.c. (chloroform/petroleum, 1:4) of the brown residue afforded several non-polar fractions (< 10 mg), but the majority of the material was very polar and showed an indistinct p.m.r. spectrum. No cyclized or phenylated material could be detected in the chromatographed materials.

Attempted alkylation of o-tolunitrile (302)

To a stirred solution of n-butyl lithium (2.5M, 0.44 ml, 1.1 mmol) in THF (6 ml) under argon at -50° was added a solution of o-tolunitrile (302) (117 mg, 1 mmol) in THF (1 ml). The bright red solution was stirred at -50° for 20 minutes, then methyl iodide (xs) was added. Immediate loss of colour was observed. The reaction mixture was poured into dichloromethane (30 ml), washed with 2NHCl (2 x 10 ml), water (2 x 10 ml) and dried. P.m.r. analysis of the resulting gum showed no material containing an ethyl group and that the nitrile (302) was present.

o-Bromobenzoyl chloride

A mixture of o-bromobenzoic acid (5.55 g, 0.028 mole) and thionyl chloride (3.5 ml, 0.05 mole) were heated with occassional shaking until evolution of HCl and SO_2 ceased. The reaction mixture was then cooled and excess thionyl chloride was distilled off. Distillation at reduced pressure gave o-bromobenzoyl chloride (5.6 g, 91%) as a light yellow oil b.p. 84° (2 mm) (lit[67] 125° (20 mm)).

2-(2-Bromo)benzoyloxyacetophenone (250 , R^1 = 2-bromophenyl)

2-Hydroxyacetophenone (249) (2.89 g, 0.021 mole) was stirred in pyridine (20 ml) and a solution of 2-bromobenzoyl chloride (5.6 g, 0.026 mole) in dry ether (20 ml) was added dropwise over a period of an hour. The mixture was stirred for 14 hours and then poured into ether (250 ml), washed with 2N hydrochloric acid solution (2 x 20 ml), water (3 x 30 ml) dried and evaporated. The resulting yellow solid was crystallised from methanol to give the ketone (250, R^1 = 2-bromophenyl) (5.37 g, 80%), as white needles m.p. 70-1° ν_{max} (nujol mull) 1730, 1675cm^{-1}. δ 2.54 (3H, s), 7.14 - 7.82 (7H, m), 8.01 - 8.20 (1H, m). (Found: M^+ 317.9888. $C_{15}H_{11}O_3{}^{79}Br$ requires M 317.9892).

1-(2-Hydroxy)phenyl-3-(2-bromo)phenylpropane-1,3-dione (251, R^1 = 2-bromophenyl)

The ketone (250, R^1 = 2-bromophenyl) (2.5 g, 7.8 mmol) and anhydrous potassium carbonate (6.43 g, 46.6 mmol) were stirred in refluxing toluene (40 ml) for 8 hours. The mixture was cooled, filtered and the solid washed well with toluene. The solid was then added to a solution of glacial acetic acid (40 g) and water (250 ml). The filtrate and washings were extracted with water (100 ml) and the extract added to the acetic acid solution. The acidic solution was washed with ethyl acetate (2 x 100 ml), and the combined organic phase dried and evaporated. The residue was dried *in vacuo* to give the dione (251, R^1 = 2-bromophenyl) (1.63 g, 65%) as a brown solid m.p. 85-6° (from ethanol) δ 6.64 (1H, s, slowly exch, olefinic enol), 6.74 - 7.73 (8H, m), 11.94 (1H, s, exch), 15.03 (1H, bs, exch). (Found: M^+ 317.9881. $C_{15}H_{11}O_3{}^{79}Br$ requires M 317.9892).

2-Methyl-3-(2-bromo)benzoylchromone (324)

The dione (251, R^1 = 2-bromophenyl) (0.6 g, 1.88 mmol), anhydrous sodium acetate (0.38 g, 4.7 mmol) and acetic anhydride (5 ml) were stirred at *ca* 115°. After 30 minutes the mixture was cooled and poured onto stirred crushed ice (10 g). After 15 minutes the mixture was extracted with dichloromethane (3 x 15 ml), washed with saturated sodium bicarbonate solution (10 ml), dried and evaporated. Crystallisation of the resulting solid from ethanol afforded the chromone (324) (0.6 g, 94 %) m.p. 157 - 8° (from ethanol) λ_{max} (ε) 300 n.m.sh. (6983), 293

(7840), 225 (23275), ν_{max} (nujol mull) 1715, 1630, 1610cm^{-1}, δ 2.60 (3H, s), 7.12 - 7.52 (7H, m), 7.94 - 8.14 (1H, m). (Found: C, 59.52; H, 3.40; Br, 23.12%. $C_{17}H_{11}O_3Br$. requires C, 59.49; H, 3.25; Br, 23.29%).

11-Hydroxy-12H-benzo [b] xanthen-12-one (248)

a) To a stirred solution of tetramethylpiperidine (0.17 ml, 1 mmol) in THF (5 ml) at -50° under argon was slowly added a solution of n-butyl lithium (2.5M, 0.4 ml, 1 mmol) in hexane. After 15 minutes a solution of the chromone (324) (114 mg, 0.3 mmol) in THF (1 ml) was added. This produced a red solution. After 2 hours at -50°, the mixture was allowed to reach room temperature and stirred for 16 hours. The mixture was then poured into dichloromethane (30 ml), washed with 2N hydrochloric acid solution (2 x 10 ml) dried and evaporated. Preparative t.l.c. (chloroform) of the residue afforded the starting chromone (324) (50 mg) and the benzoxanthenone (248) (15 mg, 19%) m.p. 197 - 201° (orange needles from petroleum - chloroform) (lit 198 - 203[14] and 205 - 209[3]) δ 7.04 - 8.38 (9H, m), 14.04 (1H, s, exch). (lit[14] δ 7.03 - 8.30 (9H, m), 14.05 (1H, s, exch).

b) The chromone (324) (686 mg, 2 mmol) was added to a solution of sodamide (from sodium, 138 mg, 6 mmol) in liquid ammonia (75 ml). After 1 hour ammonium chloride was added and the mixture warmed to room temperature. Water (15 ml) was then added and the mixture extracted with ether (3 x 25 ml), dried and evaporated. Preparative t.l.c. (chloroform) of the residue afforded the benzoxanthenone (248) (174 mg, 33%)

m.p. 207 - 9° (orange needles from petroleum/chloroform). The material was identicle (t.l.c. and p.m.r. spectrum) to that previously obtained.

2-Chloro-2′-methylbenzophenone (341)

To the stirred Grignard solution of o-bromotoluene (4.79 g, 0.028 mole) and magnesium (0.72 g, 0.03 mole) in dry ether (35 ml) was added a solution of o-chlorobenzoyl chloride (4.37 g, 0.025 mole) in dry ether (15 ml) at such a rate that the ether refluxed. After addition the mixture was refluxed for 4 hours. The brown mixture was then poured onto ice (30 g) and concentrated sulphuric acid (5 ml), extracted with ether (3 x 100 ml) washed with 1N hydrochloric acid solution (20 ml), sodium bisulphite solution (25 ml), water (20 ml), dried and evaporated. Distillation of the residue under reduced pressure afforded the ketone (341) (3.14 g, 56%) as a light yellow oil, b.p. 145 - 150°, which slowly solidified, m.p. 52-3° (lit[83] 52-3°) (from petroleum) δ 2.60 (3H s), 7.15 - 7.56 (8H, m),

Treatment of 2-chloro-2′-methylbenzophenone (341) with bases

a) To a stirred solution of tetramethylpiperidine (0.34 ml, 2 mmol) in THF (15 ml) under argon at -50° was slowly added a solution of n-butyl lithium (1.73M, 1.16 ml, 2 mmol) in hexane). After 15 minutes the mixture was warmed to -30° and a solution of the benzophenone (341) (102 mg, 0.46 mmol) in THF (2 ml) added. The deep red solution was stirred at -30° for 2 hours then warmed to room temperature for a

further hour. The mixture was poured into 2N hydrochloric acid solution (20 ml), extracted with dichloromethane (3 x 30 ml) and the organic extract dried and evaporated. P.l.c. (chloroform/petroleum :4, 3 elutions) gave small amounts (< 5 mg) of several non-polar fractions. The majority of the material was extremely polar in character and gave an indistinct p.m.r. spectrum. In none of the fractions isolated could any cyclized material be detected.

b) The benzophenone (341) (330 mg, 1.5 mmol) was added to sodamide (from sodium, 115 mg, 55 mmol) in liquid ammonia (50 ml). After 1 hour ammonium chloride was added, the mixture warmed to room temperature, and stirred with water (15 ml). The reaction mixture was extracted with ether (3 x 20 ml), and the organic phase dried and evaporated. T.l.c. and p.m.r. analysis of the reaction mixture showed that no cyclized material was present and that the starting benzophenone had been recovered in good yield (ca 80%).

2-Cyano-4-hydroxytetralone (359)

To a stirred solution of diisopropylamine (0.87 ml, 6.2 mmol) in THF (35 ml) at -40° under argon was added a solution of n-butyl lithium (2.5M, 2.48 ml, 6.2 mmol) in hexane. After 15 minutes a solution of phthalide (344) (804 mg, 6 mmol) in THF (2 ml) was added. This produced an orange solution. After 15 minutes a solution of acrylonitrile (358) (318 mg, 6 mmol) in THF (2 ml) was added and the reaction mixture immediately became yellow and very viscous. After a further 30 minutes at room temperature the mixture was warmed to room temperature over one hour. The yellow mixture was then poured into 2N hydrochloric acid solution (40 ml), extracted with ether (4 x 50 ml) and the combined extracts were dried and evaporated to afford an orange-brown gum. Trituration of this material with chloroform gave the tetralone (359) (350 mg) as a cream amorphous solid. Chromatography of the residue afforded a further quantity of the product (87 mg)(total yield, 437 mg, 39%). Sublimation in vacuo gave a white amorphous solid m.p. 116-8°. ν_{max} 3460, 2240, 1680cm^{-1}. δ (1:1 mixture of epimers) 2.56 - 2.94 (2H, m, C3-H_2), 2.75 - 3.40 (1H, bs, exch, -OH), 3.82 ($\frac{1}{2}$H, dd, J = 5, 15 Hz, exch, C2-H), 4.36 ($\frac{1}{2}$H, dd, J = 6.5, 12 Hz, exch, C2-H), 4.92 - 5.16 (1H, m, on D_2O exch. collapses to, m, $W_{\frac{1}{2}}$ 11 Hz and m, $W_{\frac{1}{2}}$ 4 Hz, C4-H), 7.25 - 8.07 (4H, m). (Found: M^+, 187.0633. $C_{11}H_{10}O_2$ requires M, 187.0633).

2-Cyano-1-naphthol (360)

The tetralone (359) (170 mg, 0.91 mmol) was dissolved in trifluoroacetic acid (TFA) (2 ml). After 20 minutes the pale green reaction mixture solidified, chloroform was added and the mixture filtered. The solid was dissolved in sodium hydroxide solution, neutralised and extracted with dichloromethane. The organic phase was dried and evaporated to give the naphthol (360) (113 mg, 74%), m.p. 176-7°, (from methanol/benzene), (lit[84]. 178°).

Methyl 3-methylbut-2-enoate (361)

Dimethyl acrylic acid (10 g, 0.10 mole), dimethyl sulphate (12.6 g, 0.10 mole) and anhydrous potassium carbonate (15.2 g, 0.11 mole) were refluxed in dry acetone (100 ml) for 2 hours, when the infra-red spectrum of the reaction mixture showed that no acid remained. The reaction mixture was filtered and the solid washed with acetone (2 x 50 ml). The filtrate was evaporated, re-dissolved in ether (100 ml), washed with 2N sodium hydroxide solution (3 x 50 ml), water (2 x 20 ml) and dried. Evaporation followed by distillation at atmospheric pressure afford the ester (361) (5.4 g, 48%) as a colourless oil, b.p. 135-7° (lit[67]., 135-8°).

2-Carbomethoxy-3,3-dimethyl-4-hydroxytetralone (362)

To a stirred solution of diisopropylamine (0.31 ml, 2.25 mmol) in THF (12 ml) under argon at -40° was slowly added a solution of n-butyl lithium (2.5M, 1.07 ml, 2.25 mmol) in hexane. After 15 minutes a solution of phthalide (344) (288 mg, 2.15 mmol) in THF (6 ml) was added. This produced an orange solution. After 15 minutes a solution of methyl 3-methylcrotonate (361) (245 mg, 2.15 mmol) in THF (1 ml) was added. After a further 30 minutes at -40° the yellow heterogeneous mixture was warmed to room temperature over one hour. The mixture was then poured into 2N hydrochloric acid solution (40 ml), extracted with ether (4 x 40 ml) and the combined extracts were dried and evaporated. Preparative t.l.c. (chloroform 2 elutions) afforded the tetralone (362) (197 mg, 37%) as a viscous yellow oil. Attempts at separation and purification were unsuccessful. P.m.r and t.l.c. showed that the material was substantially pure (~90%). ν_{max} (nujol mull) 3470, 3310, 1765, 1690cm^{-1}. δ (Isomer ratio 1:2, a :b) 1.07, 1.10, 1.16, 1.18, (6H, s, $-CH_3$), 3.15 - 3.64 (1H, bs, exch, OH), 3.74^b and, 3.76^a (3H, s, $CO_2\underline{Me}$), 3.52^a and 4.00^b (1H, s, C2-H), 4.62^a and 4.64^b (1H, s, C4-H), 7.25 - 7.66 (3H, m), 7.94 - 7.99 (1H, m). (Found: M^+, 248.1040. $C_{14}H_{16}O_4$ requires M, 248.1049).

Methyl 3,4-dimethyl-1-hydroxy-2-naphthoate (363)

A solution of the tetralone (362) (52 mg, 0.21 mmol) in dichloromethane (3 ml) was treated with boron trifluoride etherate (30 µl, 0.24 mmol). After 15 minutes the mixture was poured into water (10 ml), extracted with dichloromethane (3 x 7 ml), dried and evaporated. Preparative t.l.c. (chloroform/petroleum 1:1) afforded the naphthoate (363) (32 mg, 65%) m.p. 84-5° (needles from ethanol), λ_{max} (ε) 359 n.m. (2983), 309 (2048), 296 (2659), 285 (3019), 263 (23720), 255 (23360), 220 (27313), ν_{max} 3500 - 3000, 1650, 1585cm^{-1}, δ, 2.50 (3H, s), 2.58 (3H, s), 3.96 (3H, s), 7.32 - 7.68 (2H, m), 7.96 (1H, dd, J = 3, 10 Hz), 8.42 (1H, dd, J = 2, 10 Hz), 11.88 (1H, s, exch.). (Found: M^+ 230.0940. $C_{14}H_{14}O_3$ requires M, 230.0942).

When the preparation was repeated without isolation of the intermediate tetralone (362), the overall yield of the naphthoate (363) was 35%).

Acylation of the tetralone (362)

A solution of the tetralone (362) (380 mg, 1.53 mmol) in pyridine (3 ml) was treated with acetic anhydride (3 ml) and the mixture stirred for 16 hours. The solution was then poured into water (10 ml), and extracted with dichloromethane (3 x 25 ml). The organic extracts were then washed with 2N hydrochloric acid solution (2 x 20 ml), water (2 x

15 ml), dried and evaporated. Preparative t.l.c. (ether/petroleum, 7:3) of the residue afforded: (R_f 0.6) 4-acetoxy-2-carbomethoxy-3,3-dimethyltetralone (385) (250 mg, 56%) as an oil ν_{max} 1740, 1690cm^{-1} δ (isomer ratio 1:2, a : b) 1.15 (6H, bs), 2.10^b and 2.24^a (3H, -Ac), 3.76^a and 3.80^b (3H, s, CO_2Me), 3.60^a and 4.00^b (1H, s, C2-H), 5.96^b and 6.12^a (1H, s, C4-H), 7.25 - 7.65 (3H, m), 8.00 - 8.14 (1H, m) (Found: M^+, 290.1156. $C_{16}H_{18}O_5$ requires M, 290.1154). (R_f 0.45) Enol acetate (384) (76 mg, 15%), a light yellow oil. ν_{max} 1770, 1725, 1600cm^{-1}, δ 1.22 (3H, s), 1.26 (3H, s), 2.06 (3H, s), 2.32 (3H, s), 3.85 (3H, s), 5.75 (1H, s), 7.25 - 7.44 (4H, m). (Found: M^+, 332.1257. $C_{18}H_{20}O_6$ requires 332.1260).

2-Carbomethoxy-3,3-dimethyl-4-(2-mercaptothioethoxy)tetralone (388)

The acetate (385) (67 mg, 0.23 mmol) in dichloromethane (3 ml) was treated with ethane dithiol (387) (0.02 ml, 0.23 mmol) and boron trifluoride etherate (0.02 ml, 0.23 mmol). After 15 minutes the yellow reaction mixture was poured into saturated sodium bicarbonate solution (15 ml), extracted with dichloromethane (3 x 10 ml) and the organic phase dried and evaporated. Preparative t.l.c. (ether/petroleum 1.4, then petroleum) of the resulting yellow oil afforded the naphthoate (363) (13 mg, 25%) and the tetralone (388) (21 mg, 28%) as an oil. ν_{max} 1740, 1680cm^{-1}, δ 1.24 (3H, s), 1.34 (3H, s), 1.67 (1H, m, exch), 2.60 - 2.85 (4H, m), 3.82 (3H, s), 3.96 (1H, s), 4.18 (1H, s), 7.25 - 7.52 (3H, m), 8.02 - 8.11 (1H, m). (Found: M^+ 324.0853. $C_{16}H_{20}O_3S_2$ requires M, 324.0852).

2-Carbomethoxy-4-hydroxytetralone (365)

To a stirred solution of diisopropylamine (0.29 ml, 2.1 mmol) in THF (15 ml) at -40° under argon was slowly added a solution of n-butyl lithium (0.9M, 2.3 ml, 2.1 mmol) in hexane. After 15 minutes a solution of phthalide (344) (268 mg, 2 mmol) in THF (3 ml) was added. This produced an orange solution. After 15 minutes a solution of methyl acrylate (364) (172 mg, 2 mmol) in THF (1 ml) was added. After 45 minutes at -40° the yellow heterogeneous solution was warmed to room temperature over one hour. The mixture was then poured into 2N hydrochloric acid solution (40 ml), extracted with ether (4 x 50 ml) and the combined extracts were dried and evaporated. Preparative t.l.c. (chloroform/3% methanol) afforded the tetralone (365) (165 mg, 37%) as a viscous yellow oil. P.m.r. showed that the tetralone (365) existed mainly in the enolic form. ν_{max} 3600 - 3170, 1735, 1685, 1645, 1615, 1600, 1570cm^{-1}. δ 2.56 - 3.11 (1H, bs, exch). 2,73 (2H, d, J = 6 Hz, C3-H_2), 4.72 (1H, t, J = 6 Hz, C4-H), 7.06 - 7.72 (4H, m), 12.22 (1H, s, exch).

Methyl 1-hydroxy-2-naphthoate (366)

A solution of the tetralone (365) (87 mg, 0.4 mmol) in dichloromethane (3 ml) was treated with boron trifluoride etherate (2 drops). After 15 minutes the brown solution was poured into water (10 ml), extracted with dichloromethane (3 x 10 ml), dried and evaporated. Preparative t.l.c. (chlroform/petroleum 1:1) of the residue afforded the

naphthoate (366) (58 mg, 72%) m.p. 76-7° (from ethanol) (lit[67] 76-8°). δ 3.96 (3H, s), 7.18 - 7.76 (4H, m), 8.28 - 8.44 (1H, m), 11.82 (1H, s, exch.)

2-Carbomethoxy-4-hydroxy-3-methyltetralone (368)

To a stirred solution of diisopropylamine (0.29 ml, 2.1 mmol) in THF (15 ml) under argon at -40° was slowly added a solution of n-butyl lithium (1M, 2.1 ml, 2.1 mmol) in hexane. After 15 minutes a solution of phthalide (344) (268 mg, 2 mmol) in THF (3 ml) was added. After 15 minutes a solution of methylcrotonate (367) (200 mg, 2 mmol) in THF (1 ml) was added. After a further hour at -40°, the yellow heterogeneous mixture was warmed to room temperature over one hour. The mixture was then poured into 2N hydrochloric acid solution (40 ml), extracted with ether (4 x 50 ml) and the combined extracts were dried and evaporated. Preparative t.l.c. (chloroform - 2% methanol) of the residue afforded the tetralone (368) (224 mg, 48%) as a viscous yellow oil. ν_{max} 3540 - 3200, 1740, 1680, 1650, 1625, 1600cm^{-1}. δ (a 1:1 mixture of enol to keto tautomers, (389) : (390), a : b δ 0.78 - 1.20 (3H, d, J = 6.5 Hz ; collapses on irradiation at δ 2.6, $-CH_3$), 2.38 - 2.81 (½ H, m, C3-H^b), 2.98 - 3.18 (½ H, m, collapses to q, J = 6.5 Hz, on irradiation at δ 4.40, C3-H^a), 2.91 - 3.47 (1H, bs, exch.), 3.28 (½ H, d, J = 13 Hz, collapses to s on irradiation at δ 2.6, C2-H^b), 3.76 and 3.81 (3H, s, $-CO_2Me$), 4.40 (½ H, bs, $W_{\frac{1}{2}}$ 5 Hz, C4-H^a), 4.68 (½ H, bs, $W_{\frac{1}{2}}$ 10 Hz, collapses to s on irradiation at δ 2.6, C4-H^b), 7.11 - 7.94 (4H, m), 12.18 (½ H, s, exch. enol) (Found: M$^+$ 234.0899.

$C_{13}H_{14}O_4$ requires M 234.0892).

Methyl 1-hydroxy-3-methyl-2-naphthoate (369)

A solution of the tetralone (368) (180 mg, 0.77 mmol) in dichloromethane (10 ml) was treated with boron trifluoride etherate (3 drops). After 15 minutes the yellow-green solution was poured into water (20 ml) extracted with dichloromethane (3 x 15 ml), dried and evaporated. Preparative t.l.c. (chloroform/petroleum, 1:1) of the resulting solid afforded the naphthoate (369) (115 mg, 68%) m.p. 84-6° (from ethanol) λ_{max} (ε) 366n.m. sh. (3211) 352 (3805), 290 (3567), 280 (4350), 259 (33690), 250 (30520), 217 (22593), ν_{max} (nujol mull) 1650cm^{-1}, δ 2.53 (3H, s), 3.90 (3H, s), 6.96 (1H, s), 7.22 - 7.52 (3H, m), 8.20 - 8.32 (1H, m), 12.52 (1H, s, exch.). (Found: C, 72.23; H, 5.55%. $C_{13}H_{12}O_3$ requires C, 72.21; H, 5.60%).

2,3-Dicarbomethoxy-4-hydroxytetralone (371)

To a stirred solution of diisopropylamine (0.29 ml, 2.1 mmol) in THF (15 ml) at -40° under argon was slowly added a solution of n-butyl lithium (1M, 2.1 ml, 2.1 mmol) in hexane. After 15 minutes a solution of phthalide (344) (268 mg, 2 mmol) in THF (3 ml) was added, followed, after 15 minutes, by a solution of dimethylfumarate (370) (288 mg, 2 mmol) in THF (5 ml). After a further hour at -40° the yellow heterogeneous mixture was warmed to room temperature over one hour. The mixture was

then poured into 2N hydrochloric acid (40 ml), extracted with ether (4 x 50 ml), dried and evaporated. Preparative t.l.c. (chloroform - 2% methanol, 2 elutions) of the residue afforded the tetralone (371) (240 mg, 44%) as a viscous, light brown oil. ν_{max} 3560 - 3120, 1740, 1680, 1650, 1620, 1600, 1570cm^{-1}. δ (as 1:1 enol to keto tautomers, a : b), 3.39 - 3.82 (1H, bs, exch.), 3.52, 3.56, 3.68, 3.77, 3.82 (6H, s, $-CO_2Me$), 3.80 - 4.26 ($1\frac{1}{2}$ H, m, C-2H^b and C3-H) superimposed on multiplet, 3.94 and 4.06 (d, J = 6 and 3 Hz respectively, collapsed to s on irradiation at 5.04, C3-H^a), 5.04 (1H, bs, C4-H), 7.18 - 7.94 (4H, m), 12.40 and 12.44 ($\frac{1}{2}$ H, s, exch, enol^a). (Found: M^+ 278.0791. $C_{14}H_{14}O_6$ requires M 278.0790).

The reaction was repeated using dimethyl maleate (373). This gave the tetralone (371) (36%) essentially the same as the previous product but containing only one enol isoner. δ (1:1 mixture of enol to keto tautomers, a ; b) 2.85 - 3.24 (1H, bs, exch.), 3.58, 3.60, 3.78, 3.82, 3.84 (6H, s, CO_2Me), 3.75 - 4.22 ($1\frac{1}{2}$ H, m, C2-H^b and C3-H), superimposed on multiplet, 4.06 (d, J = 3 Hz, C3-H^a), 5.04 (1H, bs), 7.11 - 8.00 (4H, m), 12.46 ($\frac{1}{2}$ H, s, exch, enol^a).(Found: M^+ 278.0784. $C_{14}H_{14}O_6$ requires M 278.0790).

2,3-Dicarbomethoxy-1-naphthol (372)

A solution of the tetralone (371), from dimethylfumarate (370) (80 mg, 0.29 mmol) in dichloromethane (3 ml) was treated with boron trifluoride etherate (2 drops). After 15 minutes the brown solution was poured into water (10 ml), extracted with dichloromethane (3 x 10 ml), dried and evaporated. Preparative t.l.c. (chloroform/petroleum, 1:1) of the residue afforded the naphthol (372) (62 mg, 82%). m.p. 102-3° (from ethanol) λ_{max} (ε), 355 n.m. (5633), 343 (5633), 302 (2752), 290 (4117), 280 (4550), 252,sh, (32500), 249 (33367), 232 (28600), ν_{max} (nujol mull) 3400 - 3000, 1720, 1685cm^{-1}, δ 3.88 (3H, s), 3.92 (3H, s), 7.36 (1H, s, C4-H), 7.42 - 7.70 (3H, m), 8.22 - 8.38 (1H, m, C8-H), 11.68 (1H, s, exch.), (Found: C, 64.18; H, 4.66%; M^+ 260.0672. $C_{14}H_{12}O_5$ requires C, 64.61; H, 4.65%; M 260.0684).

Repeating the reaction with the tetralone (371, from dimethyl maleate (373)) afforded the naphrhol (372) (78%) identical in all respects to the product previously obtained.

2,3-Dicarbomethoxy-1,4-dihydro-1-naphthol (396) was prepared according to the method of Arnold[2].

Oxidation of 2,3-dicarbomethoxy-1,4-dihydro-1-naphthol (396)[1]

A solution of the diester (396) (262 mg) in benzene (10 ml) was stirred with manganes dioxide (1 g, excess) for 12 hours. The mixture was then filtered and the solid washed well with benzene. Evaporation and preparative t.l.c. (benzene - acetone, 9:1) of the residue afforded:-

2,3-Dicarbomethoxynaphthalene (397) (100 mg, 42%) m.p. 48-9° (from ether/petroleum) (lit[1], 49-50°).

Dimeric napthol (398) (70 mg, 13%) m.p. 240-6 dec (needles from benzene) ν_{max} (nujol mull) 1730, 1665cm^{-1}, δ 3.45 (3H, s), 3.96 (3H, s), 7.20 - 7.72 (3H, m), 8.50 - 8.65 (1H, m), 13.00 (1H, s, exch.). (Found: C, 65.09; H, 4.57; M^+ 518.1215. $C_{28}H_{22}O_{10}$ requires C, 64.86; H, 4.28; M 518.1213).

3-(2,2-Dicarbomethoxy-1-methylethyl)phthalide (375)

To a stirred solution of diisopropylamine (0.29 ml, 2.1 mmol) in THF (10 ml) under argon at -40° was slowly added a solution of n-butyl lithium (2.5M, 0.84 ml, 2.1 mmol) in hexane. After 15 minutes a solution of phthalide (344) (236 mg, 2 mmol) in THF (8 ml) was added, followed, after 15 minutes by a solution of dimethylethylidenemalonate (374) (316 mg, 2 mmol) in THF (2 ml). After a further 2 hours at -40° the yellow solution was warmed to room temperature over one hour. The mixture was then poured into 2N hydrochloric acid solution (40 ml), extracted with ether (4 x 50 ml), dried and evaporated. Preparative t.l.c.

(chloroform, 2 elutions) of the residue afforded the phthalide (375) (264 mg, 45%) as a viscous yellow oil. ν_{max} 1755, 1730cm^{-1}. δ (as 1:2 epimer mixture, a : b) 0.62^{b} and 1.26^{a} (3H, d, J = 7.5 Hz, collapsed to s on irradiation at δ 2.95, Me) 2.82 - 3.16 (1H, m, C1'-H), 3.64^{a}, 3.68^{a}, 3.76^{b}, 3.82^{b} (6H, s, CO_2Me), 5.54^{a} and 5.70^{b} (1H, d, J = 6.0 and 1.5 Hz respectively, collapsed to s on irradiation at δ 2.95, C3-H), 7.37 - 7.95 (4H, m). C2'-H obscurred by CO_2Me envelope. (Found: M^+ 292.0944. $C_{15}H_{16}O_6$ requires M 292.0947).

3-(1,1-dimethyl-3-oxobutyl)phthalide (377)

To a stirred solution of diisopropylamine (0.29 ml, 2.1 mmol) in THF (15 ml) under argon at -40° was slowly added a solution of n-butyl lithium (2.1M, 1 ml, 2.1 mmol) in hexane. After 15 minutes a solution of phthalide (344) (268 mg, 2 mmol) in THF (5 ml) was added, followed, after 15 minutes, by a solution of mesityl oxide (376) (196 mg, 2 mmol) in THF (1 ml). After a further hour at -40°, the yellow solution was warmed to room temperature over an hour. The mixture was then poured into 2N hydrochloric acid solution (40 ml), extracted with ether (4 x 50 ml), dried and evaporated. Preparative t.l.c. (chloroform) of the residue afforded the phthalide (377) (95 mg, 20%) as a viscous yellow oil. ν_{max} 1725, 1685cm^{-1}, δ 1.03 (3H, s), 1.10 (3H, s), 2.16 (3H, s, CO_2Me), 2.48 and 2.90 (2H, centres of ABq, J = 18 Hz, C2'-H_2), 5.97 (1H, s, C3-H), 7.36 - 7.64 (3H, m), 7.98 - 8.15 (1H, m). (Found: M^+ 232.1102. $C_{14}H_{16}O_4$ requires M 232.1099).

Reaction of phthalide (344) with ethyl 3-ethoxycrotonate (378)

To a stirred solution of diisopropylamine (0.29 ml, 2.1 mmol) in THF (15 ml) under argon at -40° was slowly added a solution of n-butyl lithium (2.5M, 0.84 ml, 2.1 mmol) in hexane. After 15 minutes a solution of phthalide (344) (268 mg, 2 mmol) in THF (3 ml) was added, followed, after 15 minutes, by a solution of the ester (378) (319 mg, 2 mmol). After a further 2 hours at -40° the red solution was warmed to room temperature over an hour. The mixture was poured into 2N hydrochloric acid solution (40 ml) extracted with ether (4 x 50 ml), dried and evaporated. P.m.r. analysis of the resulting brown oil revealed that the ester (378) was the major component and that the phthalide (344) had been consumed. No resonances corresponding to the tetralone (409) were observed.

Reaction of phthalide (344) with crotonolactone (379)

To a stirred solution of diisopropylamine (0.29 ml, 2.1 mmol) in THF (15 ml) under argon at -40° was slowly added a solution of n-butyl lithium (1M, 2.1 ml, 2.1 mmol) in hexane. After 15 minutes a solution of phthalide (344) (268 mg, 2 mmol) in THF (3 ml) was added, followed, after 15 minutes, by a solution of crotonolactone (379)(168 mg, 2 mmol) in THF (1 ml). After a further hour at -40° the yellow heterogeneous solution was warmed to room temperature over an hour. The mixture was then poured into 2N hydrochloric acid solution (40 ml), extracted with ether (4 x 50 ml), dried and evaporated. Preparative t.l.c. (chloroform -

2% methanol, then 2 elutions of 5% mixture) of the brown residue afforded material having an indistinct p.m.r. spectrum.

6-Methoxyphthalide (411) was prepared according to the method of Chakravarti and Perkin[70] from m-methoxybenzoic acid in yield of 8%. The product was purified by chromatography on silica (chloroform - ethyl acetate, 9:1) and had m.pt. 120° (from water) (lit[70] 120°) λ_{max} (ε) 300 n.m. (2414, 232 sh. (4692), 221 (4738), δ 3.85 (3H, s), 5.22 (3H, s), 7.10 - 7.36 (3H, m).

2-Carbomethoxy-3,3-dimethyl-4-hydroxy-7-methoxytetralone (412)

To a stirred solution of diisopropylamine (0.15 ml, 1.05 mmol) in THF (10 ml) under argon at -40° was slowly added a solution of n-butyl lithium (1M, 1.05 ml, 1.05 mmol) in hexane. After 15 minutes a solution of 6-methoxyphthalide (411) (164 mg, 1 mmol) in THF (1 ml) was added. This produced an orange solution. After 15 minutes a solution of methyl 3-methylcrotonate (361) (114 mg, 1 mmol) in THF (1 ml) was added. After a further 30 minutes at -40°, the yellow heterogeneous mixture was warmed to room temperature over an hour. The mixture was then poured into 2N hydrochloric acid (20 ml), extracted with dichloromethane (4 x 25 ml), dried and evaporated. Preparative t.l.c. (chloroform - 3% methanol) afforded the tetralone (412) (115 mg, 41%) as a viscous yellow oil. ν_{max} 3600, 3225, 1750, 1690cm^{-1}. δ (isomer ratio 1:2, a : b) 1.08, 1.12, 1.15 (total 6H, s, Me), 2.60 - 2.96 (1H, bs, exch.) 3.45[a]

and 3.96[b] (1H, s, C2-H), 3.75 (3H, s), 3.80 (3H, s), 4.46[a] and 4.52[b] (1H, s, C4-H), 7.00 - 7.45 (3H, m). (Found: M^+ 278.1177. $C_{15}H_{18}O_5$ requires M 278.1154).

Methyl 3,4-dimethyl-1-hydroxy-7-methoxy-2-naphthoate (413)

A solution of the tetralone (412) (80 mg, 0.29 mmol) in dichloromethane (5 ml) was treated with boron trifluoride etherate (2 drops). After 15 minutes the brown solution was poured into water (10 ml), extracted with dichloromethane (3 x 10 ml), dried and evaporated Preparative t.l.c. (ether - petroleum, 1:1) of the residue afforded the naphthoate (413) (38 mg, 51%) m.p. 103-4° (from ether - petroleum), λ_{max} (ε) 373n.m. (2364, 296sh. (5910), 274 (18909), 238 (23636), υ_{max} 1650cm^{-1}, δ 2.44 (3H, s), 2.48 (3H, s), 3.90 (3H, s), 3.96 (3H, s), 7.14 (1H, dd, J = 3, 9 Hz), 7.60 (1H, d, J = 3 Hz), 7.72 (1H, d, J = 9 Hz), 11.64 (1H, s, exch.). (Found: C, 69.53; H, 6.19%; M^+ 260.1047. $C_{15}H_{15}O_4$ requires C, 69.48; H, 5.83%; M. 260.1055).

4-Hydroxphthalide was prepared according to the method Bueller et.al[71]. Hydrogen chloride was passed into a stirred solution of m-hydroxybenzoic acid (25 g, 0.18 mole), 40% formaldehyde solution (500 ml), concentrated hydrochloric acid (500 ml) and concentrated sulphuric acid (25 ml) at 30-40° for 2 hours. The mixture was then cooled and the preciptate filtered to give 4-hydroxyphthalide (5.5 g), m.p. 253-4° (from H_2O) (lit[71] 254°) δ ($CDCl_3$ - d_6-DMSO) 3.00 - 4.02 (1H, bs, exch.), 5.26

(2H, s), 6.96 - 7.33 (3H, m).

The filtrate was diluted with water and stood overnight. The resulting precipitate was filtered to give the phthalide (242 or 243) (4 g) m.p. 177-9° (feathers from water) (lit[71] 175°) λ_{max} (ε) 304n.m. (1776), 228sh. (3744), 220 (5520), ν_{max} (nujol mull) 1740cm^{-1}, δ (d_6-acetone) 5.20 (2H, s), 5.34 (4H, s), 7.18 (1H, d, J = 8 Hz), 7.46 (1H, d, J = 8 Hz). (Found: M^+ 192.0422. $C_{10}H_8O_4$ requires M 192.0423).

4-Methoxyphthalide (414) was prepared according to the method of Bueller et.al[71] from 4-hydroxyphthalide. (414) m.p. 125-6° (lit[71] m.p. 127°), λ_{max} (ε) 293n.m. (1565), 233sh. (3615), 220 (4435), ν_{max} 1735cm^{-1}, δ 3.90 (3H, s), 5.22 (2H, s), 6.98 - 7.14 (1H, m), 7.34 - 7.52 (2H, m).

2-Carbomethoxy-3,3-dimethyl-4-hydroxy-5-methoxytetralone (415)

To a stirred solution of diisopropylamine (0.29 ml, 2.1 mmol) in THF (15 ml) under argon at -40° was slowly added a solution of n-butyl lithium (0.9M, 2.3 ml, 2.1 mmol) in hexane. After 15 minutes a solution of 4-methoxyphthalide (414) (328 mg, 2 mmol) in THF (3 ml) was added. This produced a green solution. After 15 minutes a solution of methyl 3-methylcrotonate (361) (228 mg, 2 mmol) in THF (1 ml) was added. After a further 30 minutes at -40° the yellow heterogeneous mixture was warmed to room temperature over an hour. The mixture was then poured into 2N hydrochloric acid solution (40 ml), extracted with ether (4 x 50 ml), dried and evaporated. Preparative t.l.c. (chloroform - ethyl acetate, 9 : 1) of the residue afforded the tetralone (415), (269 mg, 48%) as a

viscous yellow oil. ν_{max} 3620 - 3250, 1740, 1685, 1585cm^{-1}, δ 1.08 (3H, s), 1.24 (3H, s), 2.90 - 3.18 (1H, bs, exch.), 3.76 (3H, s), 3.86 (3H, s), 4.10 (1H, s, C2-H), 4.78 (1H, s, C4-H), 7.06 (1H, d, J = 7.5 Hz), 7.28 (1H, t, J = 7.5 Hz), 7.50 (1H, d, J = 7.5 Hz). (Found: M$^+$ 278.1161. $C_{15}H_{18}O_5$ requires M 278.1154)

Methyl 3,4-dimethyl-1-hydroxy-5-methoxy-2-naphthoate (416)

A solution of the tetralone (415) (182 mg, 0.65 mmol) in dichloromethane (5 ml) was treated with boron trifluoride etherate (3 drops). After 10 minutes the brown solution was poured into water (15 ml), extracted with dichloromethane (3 x 10 ml), dried and evaporated. Preparative t.l.c. (chloroform - petroleum, 1:1) of the residue afforded the naphthoate (416) (91 mg, 51%) m.p. 93-4° (from ethanol), λ_{max} (ε) 371n.m. (2311), 347sh. (1878), 313 (2781), 301 (2708, 299 (2600), 253 (21667), 222 (33222), ν_{max} (nujol mull), 1650, 1585cm^{-1}, δ 2.40 (3H, s), 2.60 (3H, s), 3.77 (3H, s), 3.86 (3H, s), 6.78 (1H, d, J = 7.5 Hz), 7.17 (1H, t, J = 7.5 Hz), 7.88 (1H, d, J = 7.5 Hz), 11.40 (1H, s, exch.). (Found: M$^+$ 260.1055. $C_{15}H_{16}O_4$ requires M 260.1049).

2-Carbomethoxy-4-hydroxy-5-methoxy-3-methyltetralone (417)

To a stirred solution of diisopropylamine (0.29 ml, 2.1 mmol) in THF (15 ml) under argon at -40° was slowly added a solution of n-butyl lithium (0.9M, 2.3 ml, 2.1 mmol) in hexane. After 15 minutes a solution of 4-methoxyphthalide (414) (328 mg, 2 mmol) in THF (4 ml) was added,

followed after 15 minutes, by a solution of methylcrotonate (376) (200 mg, 2 mmol) in THF (1 ml). After a further hour at -40°, the yellow heterogeneous mixture was warmed to room temperature over an hour. The mixture was then poured into 2N hydrochloric acid solution (40 ml), extracted with ether (4 x 50 ml), dried and evaporated. Preparative t.l.c. (chloroform - 5% methanol) of the residue afforded the tetralone (417) (309 mg, 58%) as a viscous yellow oil. ν_{max} 3620 - 3160, 1730, 1680, 1645, 1615, 1580cm^{-1}. δ (1:1 mixture of enol to keto tautomers, (425) : (426), a ; b), 0.85^{b}, 1.07^{a} (3H, d, J = 7.5 Hz), 2.14 - 2.54 ($\frac{1}{2}$ H, m, collapses to ill-defined d, J = 13 - 14 Hz, on irradiation at δ 0.85, C3-H^{b}), 2.60 - 3.14 (1H, bs, exch.), 2.91 - 3.12 ($\frac{1}{2}$ H, m, collapses to bs, $W_{\frac{1}{2}}$, 3 Hz, on irradiation at δ 1.07, C3-H^{a}), 3.68 (3H, s), 3.74 (3H, s), 4.74 ($\frac{1}{2}$ H, bs, $W_{\frac{1}{2}}$ 3 Hz, sharpens on irradiation at δ 3.00, C4-H^{a}), 4.90 (1H, d, J = 2 Hz, collapses to s on irradiation at δ 2.35, C4-H^{b}), 6.81-7.44 (3H, m), 12.08 ($\frac{1}{2}$ H, s, exch, enol^{a}). (Found: M^{+} 264.0969. $C_{14}H_{16}O_5$ requires M 264.0997).

Methyl 1-hydroxy-5-methoxy-3-methyl-2-naphthoate (418)

A solution of the tetralone (417) (200 mg, 0.76 mmol) in dichloromethane (5 mls) was treated with boron trifluoride etherate (3 drops). After 10 minutes the brown solution was poured into water (15 ml), extracted with dichloromethane (3 x 10 ml), dried and evaporated. Preparative t.l.c. (chloroform - petroleum, 1:1) of the residue afforded the naphthoate (418) (81 mg, 43%) m.p. 154-5° (from ether-petroleum), λ_{max} (ε) 370n.m. sh. (3536), 362 (3844), 307 (3075, 294 (2952),

282 (3014), 252 (33825), 218 (13226), ν_{max} 1645, 1580cm^{-1}, δ 2.62 (3H, s), 3.94 (6H, s), 6.81 (1H, d, J = 7.5 Hz), 7.24 (1H, t, J = 7.5 Hz), 7.40 (1H, s), 7.82 (1H, d, J = 7.5 Hz), 11.40 (1H, s, exch.). (Found: C, 68.30; H, 5.71%. $C_{14}H_{14}O_4$ requires C, 68.28; H, 5.73%).

2,3-Dicarbomethoxy-4-hydroxy-5-methoxytetralone (419)

To a stirred solution of diisopropylamine (0.29 ml, 2.1 mmol) in THF (15 ml) under argon at -40° was slowly added a solution of n-butyl lithium (0.9M, 2.3 ml, 2.1 mmol) in hexane. After 15 minutes a solution of 4-methoxyphthalide (414) (328 mg, 2 mmol) in THF (5 ml) was added, followed, after 15 minutes, by a solution of dimethyl maleate (373) (288 mg, 2 mmol) in THF (1 ml). After a further hour at -40° the orange heterogeneous mixture was warmed to room temperature over an hour. The mixture was then poured into 2N hydrochloric acid solution (40 ml), extracted with ether (4 x 50 ml), dried and evaporated. Preparative t.l.c. (chloroform - 3% methanol) of the residue afforded the tetralone (419) (209 mg, 34%) as a viscous yellow oil. ν_{max} 3600 - 3200, 1735, 1690, 1655, 1630, 1580cm^{-1}, δ (as 3:2 mixture of enol to keto tautomers, (427) : (428), a ; b) 2,72 - 3.33 (1H, bs, exch.), 3.56, 3.74, 3.82, 3.87 (9H, s), 3.6 - 3.8 (2/5H, m, C3-H^b), 4.08 (3/5H, bs, $W_{\frac{1}{2}}$ 4.5 Hz, C3-H^a), 4.28 (2/5H, d, J = 12 Hz, exch. C2-H^b), 5.46 (3/5H, bs, $W_{\frac{1}{2}}$ 6 Hz, sharpens to bs, $W_{\frac{1}{2}}$ 4.5 Hz on exch. C4-H^a), 5.60 (2/5H, bs, $W_{\frac{1}{2}}$ 7 Hz, sharpens to d, J = 4.5 Hz on exch. C4-H^b), 6.84 - 7.55 (3H, m), 12.36 (3/5H, s, exch.) (Found: M$^+$ 308.0910. $C_{15}H_{16}O_7$ requires M 308.0896).

2,3-Dicarbomethoxy-5-methoxy-1-naphthol (420)

A solution of the tetralone (419) (190 mg, 0.62 mmol) in benzene (6 ml) containing a trace of toluene-p-sulphonic acid was refluxed for one hour. The mixture was then cooled and evaporated. Preparative t.l.c. (chloroform - petroleum, 3:2, 2 elutions) of the residue afforded the naphthol (420) (120 mg, 67%) m.p. 106-7° (from ether - petroleum) λ_{max} (ε) 366n.m. (4930), 354 (5111), 310 (3009), 299 (2610), 249 (38063), 224 (34438), ν_{max} (nujol mull), 1725, 1665cm^{-1}, δ 3.88 (3H, s), 3.92 (6H, s), 6.90 (1H, d, J = 7.5 Hz), 7.38 (1H, t, J = 7.5 Hz), 7.78 (1H, s), 7.86 (1H, d, J = 7.5 Hz), 11.58 (1H, s, exch.). (Found: C, 61.96; H, 4.88%. $C_{15}H_{14}O_6$ requires C, 62.03, H, 4.86%).

4-Hydroxy-3-hydroxymethyl-5-methoxytetralone-2-carboxylic acid δ-lactone (421)

To a stirred solution of diisopropylamine (0.29 ml, 2.1 mmol) in THF (15 ml) at -40° under argon was added a solution of n-butyl lithium (0.9M, 2.3 ml, 2.1 mmol) in hexane. After 15 minutes a solution of 4-methoxyphthalide (414) (328 mg, 2 mmol) in THF (3 ml), followed, after 15 minutes, by a solution of crotonolactone (379) (168 mg, 2 mmol) in THF (1 ml). After a further hour at -40° the yellow-green heterogeneous mixture was warmed to room temperature over an hour. The mixture was then poured into 2N hydrochloric acid solution (40 ml), extracted with ether (4 x 50 ml), dried and evaporated. Trituration of the orange residue with dichloromethane afforded the tetralone (421) (150 mg, 30%)

as an amorphous solid m.p. 164-6°, ν_{max} (nujol mull) 3450-3120, 1760, 1655, 1585cm^{-1}, δ (d_6-acetone/d_6-DMSO) 2.98 - 3.30 (2H, m, collapses to 1H, m on exch, C3-H, OH), 3.68 - 3.80 (1H, impartially obscurred, C2-H), 3.90 (3H, s), 4.36 - 4.66 (2H, m, sharpens on irradiation at δ 3.15), 5.40 (1H, bs, collapses to d, J = 3 Hz on exch., which collapses to s on irradiation at δ 3.15, C4-H), 7.20 - 7.48 (3H, m), (Found M^+ 248.0683. $C_{13}H_{12}O_5$ requires M 248.0685).

1-Hydroxy-3-hydroxymethyl-5-methoxy-2-naphthoic acid α-lactone (422)

The tetralone (421) (100 mg, 0.4 mmol) was dissolved in TFA (1 ml). After 5 minutes the mixture solidified. The mixture was dissolved in sodium carbonate, neutralized with 2N HCl and extracted with dichloromethane (3 x 10 ml). The dried organic phase was evaporated to give the naphthol lactone (422) (48 mg, 52%) m.p. 205 - 6° (from chloroform - petroleum) ν_{max} (CH_2Cl_2) 3400, 1728cm^{-1} δ 4.08 (3H, s), 5.50 (2H, s), 7.09 (1H, d, J = 8 Hz), 7.56 (1H, t, J = 8 Hz, 7.86 (1H, s), 8.03 (1H, d, J = 8 Hz), 8.60 (1H, s, exch.). (Found: M^+ 230.0583. $C_{13}H_{10}O_4$ requires M 230.0579).

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