REACTIONS OF PHTHALIDE ORTHO ESTERS WITH DIENOPHILES: SYNTHESIS OF NAPHTHALENES AND HOMOQUINONES

by

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SYNTHESIS OF NAPHTHALENES
AND HOMOQUINONES

To Amanda, Andreina, José Luis and my father.

DOCTOR OF PHILOSOPHY (1980)
(Chemistry)

McMASTER UNIVERSITY
Hamilton, Ontario

TITLE: Reactions of Phthalide Ortho Esters with Dienophiles: Synthesis of Naphthalenes and Homoquinones

AUTHOR: Luis Contreras, Lic. Quim. (Central University of Venezuela, Caracas)

SUPERVISOR: Professor D. B. MacLean

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ABSTRACT

A new reaction between phthalide ortho esters with a series of dienophiles has been studied. It was found that treatment of 1,1-diethoxyphthalan or 5,6-dimethoxy-1,1-diethoxyphthalan with activated acetylenes yielded tetrasubstituted naphthalenes. Reaction of 1,1-diethoxyphthalan with diethyl maleate afforded a mixture of enol ethers and a trisubstituted naphthalene. The enol ethers were converted into a disubstituted naphthol under acidic conditions. Treatment of phthalide ortho esters with 1,4-benzoquinone or 1,4-naphthoquinone gave p-homoquinones instead of the expected linear tricyclic and tetracyclic aromatic compounds.

The formation of the compounds derived from the reaction of phthalide ortho esters with dienophiles has been rationalized in terms of a mechanism that involves 1-ethoxyisobenzofurans as intermediates.

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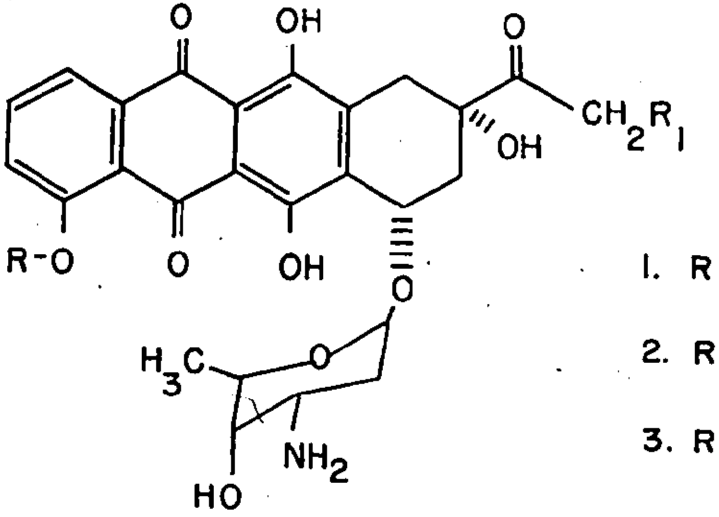
CHAPTER 1

HISTORICAL INTRODUCTION

1.1 Introduction

Functionalized naphthalenes are important intermediates in the synthesis of numerous naturally occurring compounds of biological importance. Such systems include naphthoquinones (1), anthraquinones (1), and anthracycline antitumour and antibiotic agents (2), most notably, adriamycin 1, daunomycin 2, and carminomycin 3.



1. R = CH_3 , R_1 = OH
2. R = CH_3 , R_1 = H
3. R = H , R_1 = H .

The general methods that have been employed to construct linear polynuclear aromatic systems are:

(i) Friedel-Crafts alkylations or acylations,

(ii) nucleophilic condensations,

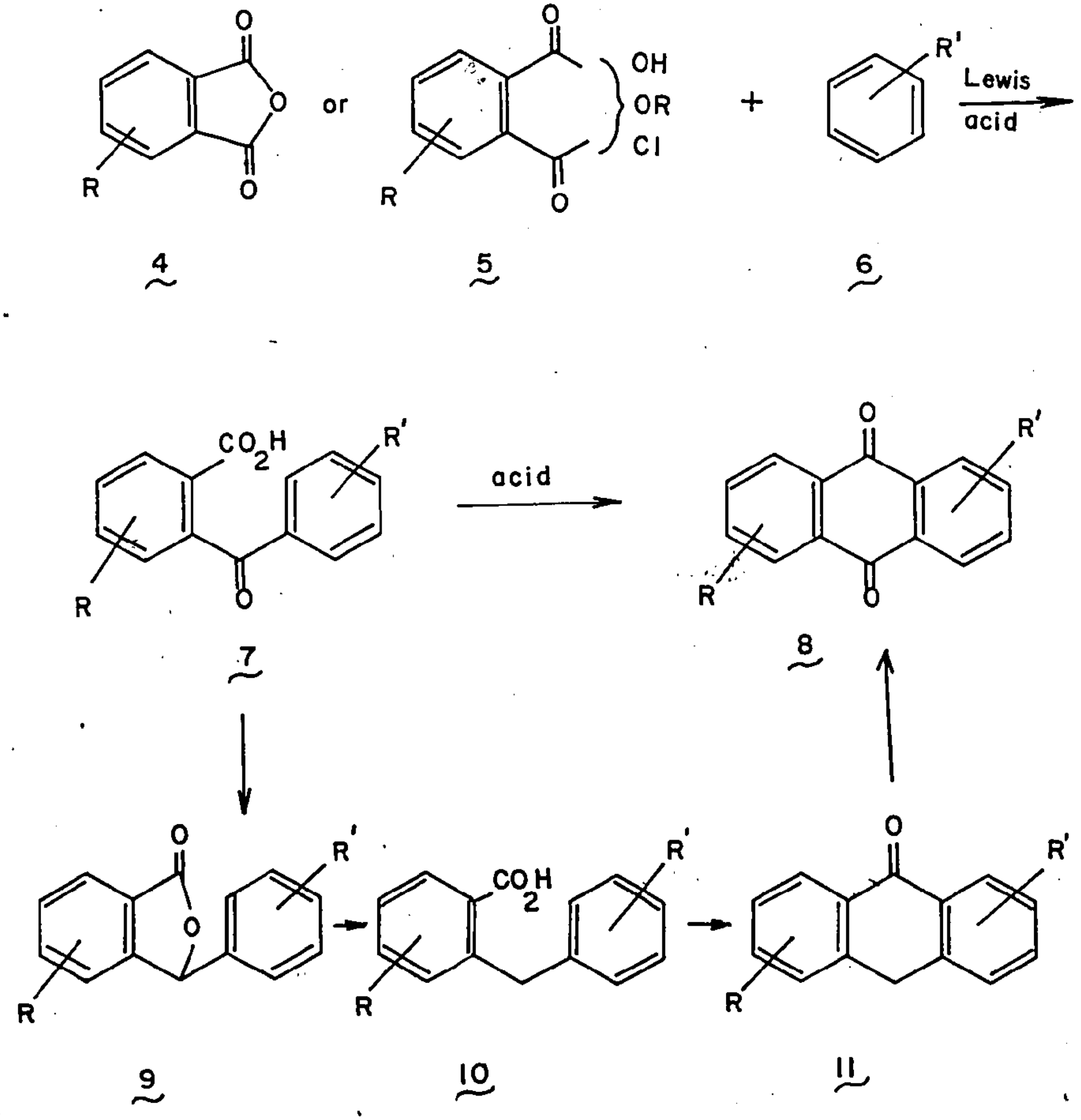
(iii) various forms of the Diels-Alder reaction, and,

(iv) cyclization of polyketides.

Each of the general methods will be reviewed in this chapter.

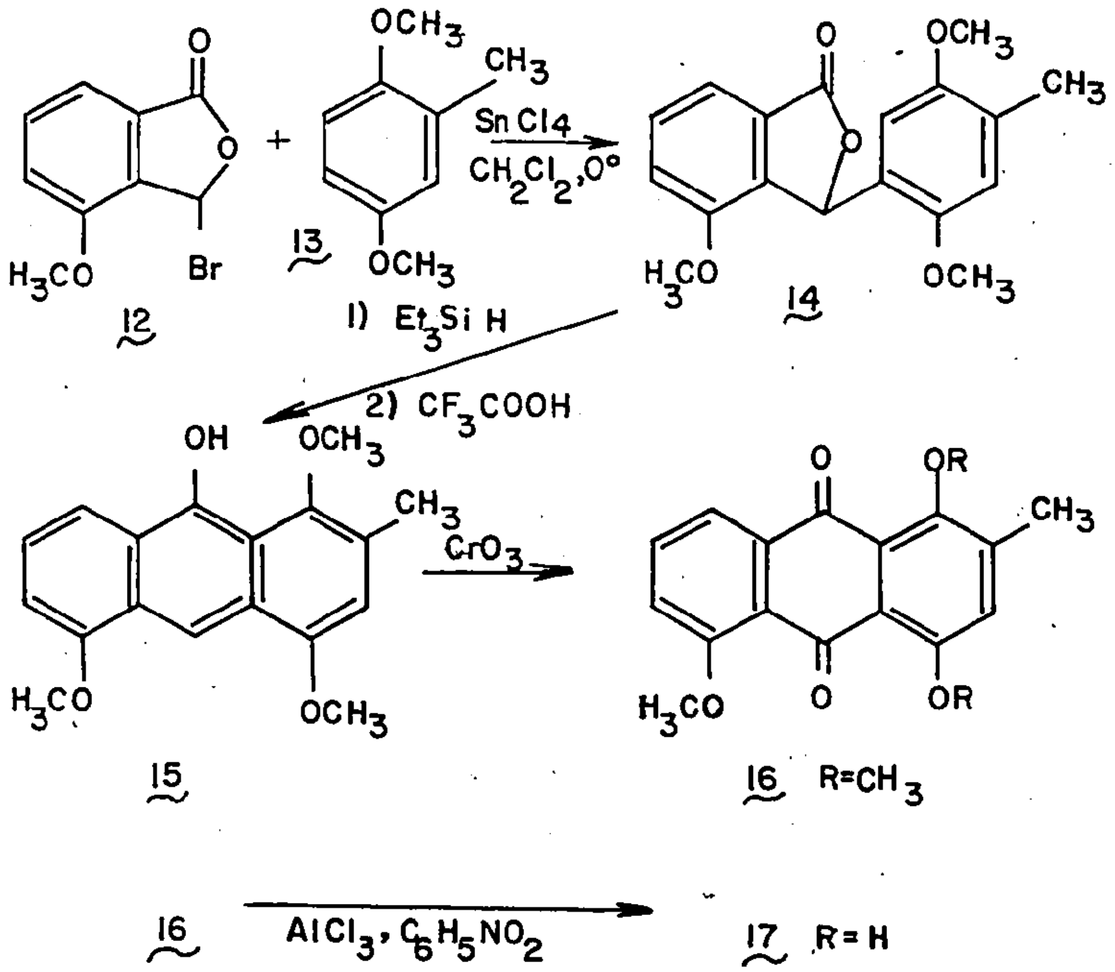
1.2 Friedel-Crafts Type Routes

Friedel-Crafts acylation has been the traditional procedure for the synthesis of polycyclic aromatic compounds. Thus, the synthesis of anthraquinones and higher analogues is often accomplished by acylation of aromatic substrates with phthalic anhydrides or phthalic acid derivatives in two discrete steps. However, the method suffers from a lack of regiospecificity when the aromatic substrate 6 and anhydride 4 or phthalic acid 5 are both substituted (3). In many cases, acylation (7 → 8) is accompanied by the Hayashi rearrangement (4) and is difficult to accomplish unless the aromatic substrate is activated. These difficulties may be avoided by reduction of 7 first to 9 and then to 10, before cyclization to 11. Finally, oxidation of 11 to 8 may be brought about, as shown in Scheme 1.


O
O
O
R
or
O
O
OH
OR
Cl
R
+
R'
Lewis
acid
4
5
6
CO2H
R'
R
O
acid
O
O
R'
R
7
8
O
O
R'
R
CO2H
R'
R
O
R'
R
9
10
11

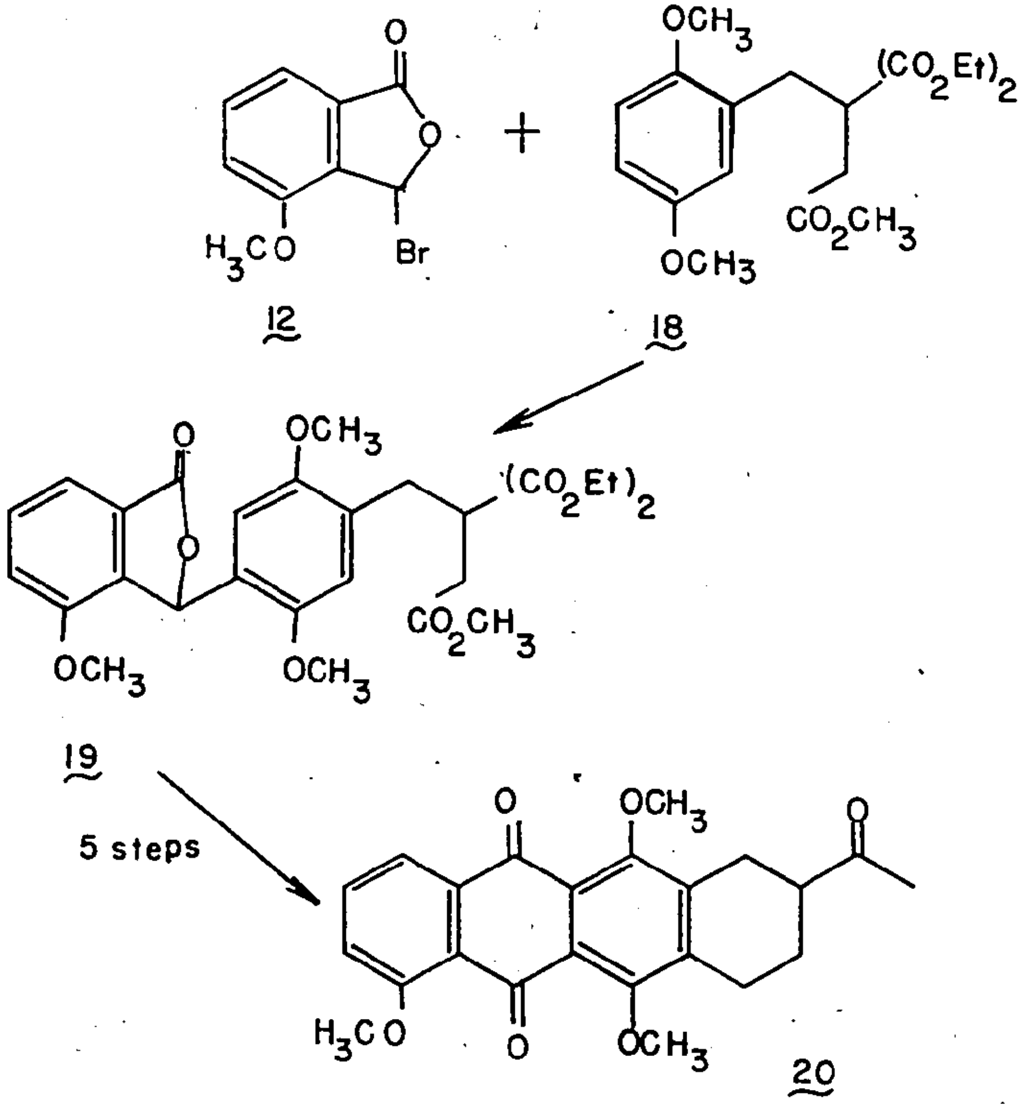
Scheme 1

In order to overcome the lack of regiospecificity in the preparation of compounds such as <u>9</u>, Johnson et al. (5) have recently developed a regiospecific synthesis of 3-arylphthalides <u>14</u> from the reaction of 3-bromophthalide <u>12</u>, with an aromatic substrate, e.g., <u>13</u>, in the presence of stannic chloride (Scheme 2).



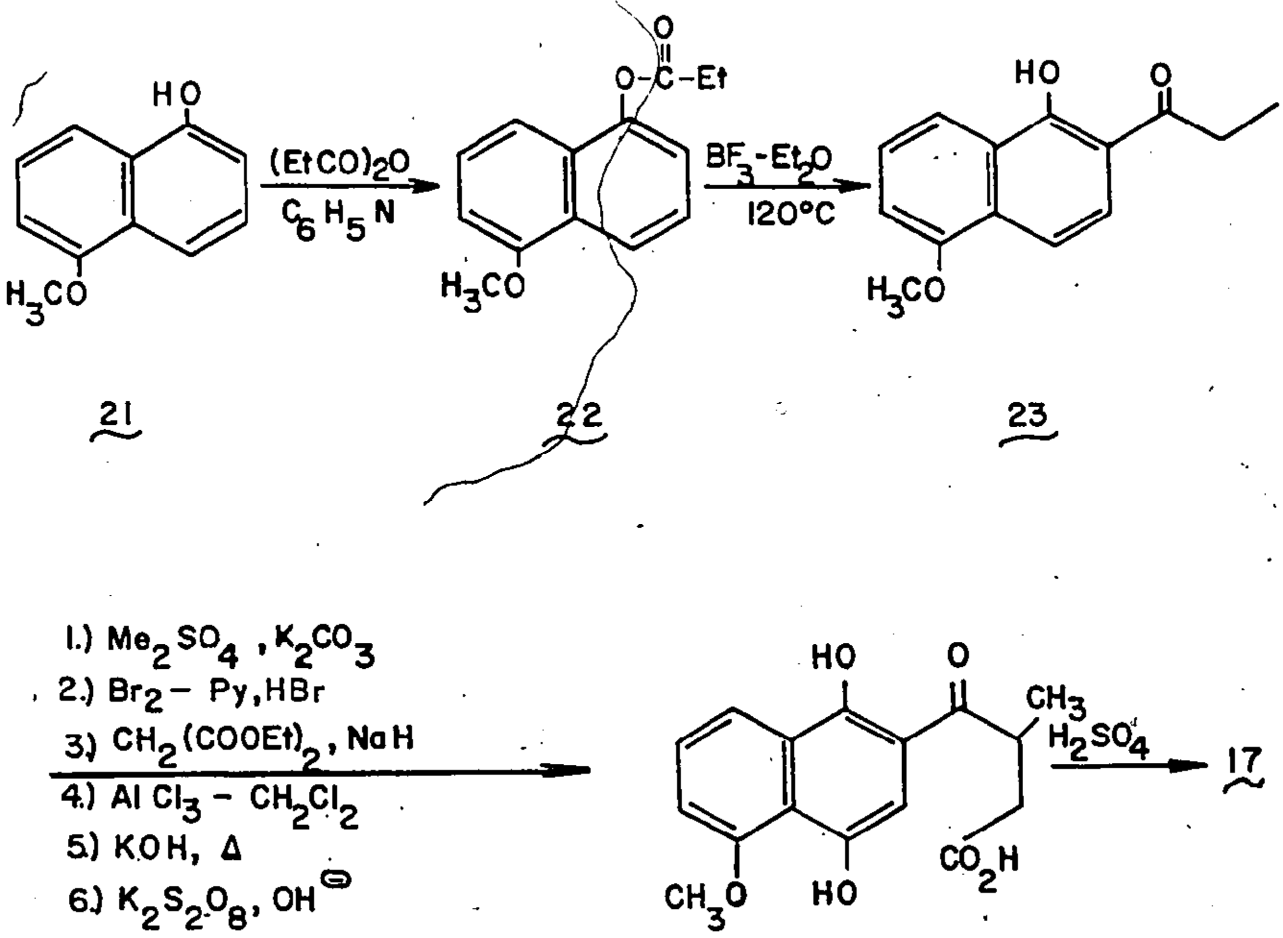
<u>Scheme 2</u>

Compounds such as 14 were converted to islandicin 17, as shown in Scheme 2. Johnson et al. (6) have also extended this method to the synthesis of anthracyclinones, such as 20, as shown in Scheme 3.



Scheme 3

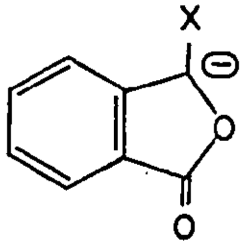
Sih et al. (7) have reported an alternative approach to islandicin 17. They prepared 22 by acylation of 1-hydroxy 5-methoxynaphthalene 21. Fries rearrangement of 22 proceeded regiospecifically in 80% yield to 23. Further chemical transformations of 23 afforded islandicin 17 (Scheme 4).



Scheme 4

1.3 Nucleophilic Condensations

Recently, a number of new methods have been developed for the construction of polynuclear aromatic systems. Most of these methods involve the use of phthalide anions 24 as key intermediates.

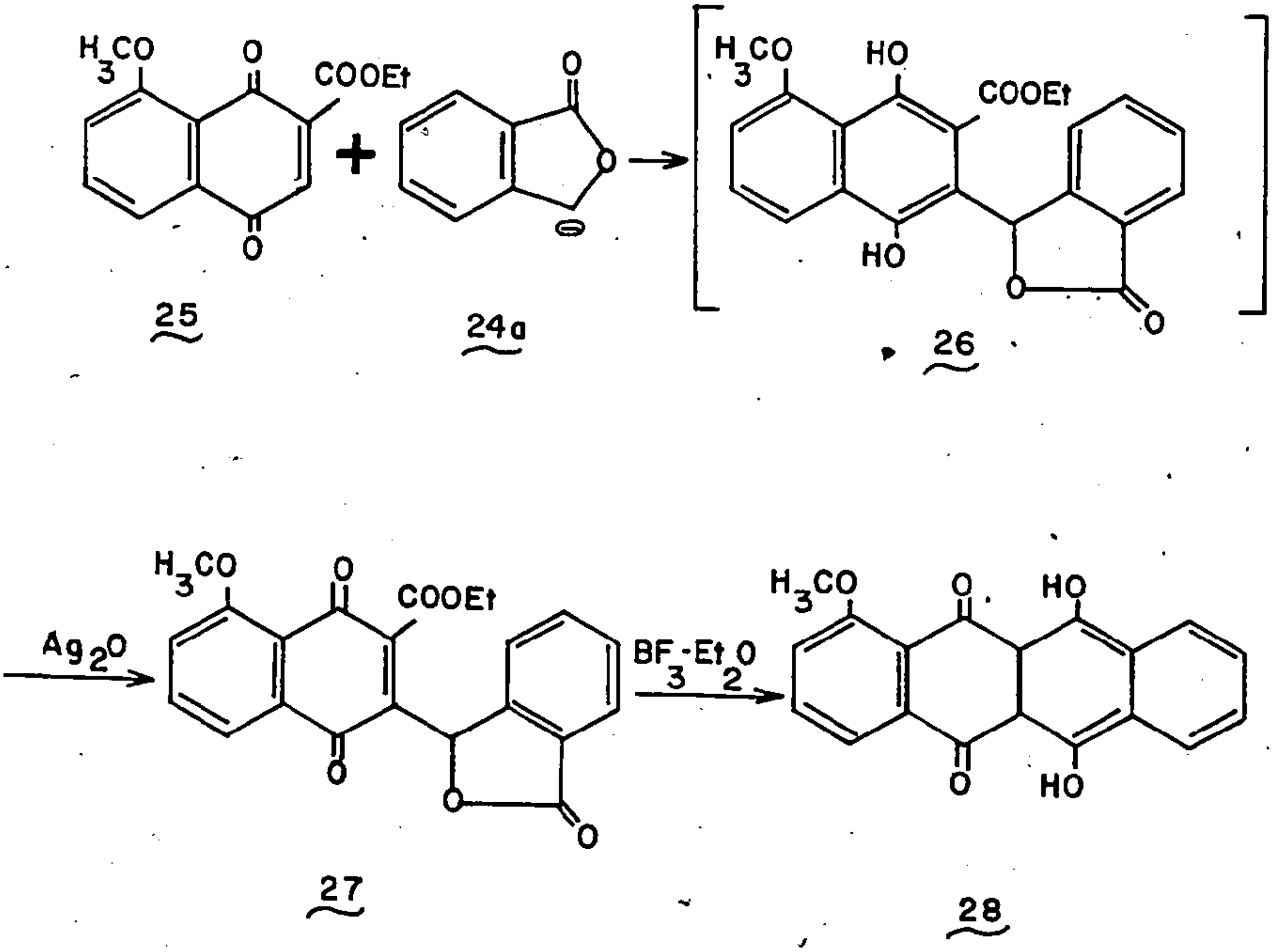


24a. X = H

24b. X = SO_2Ar

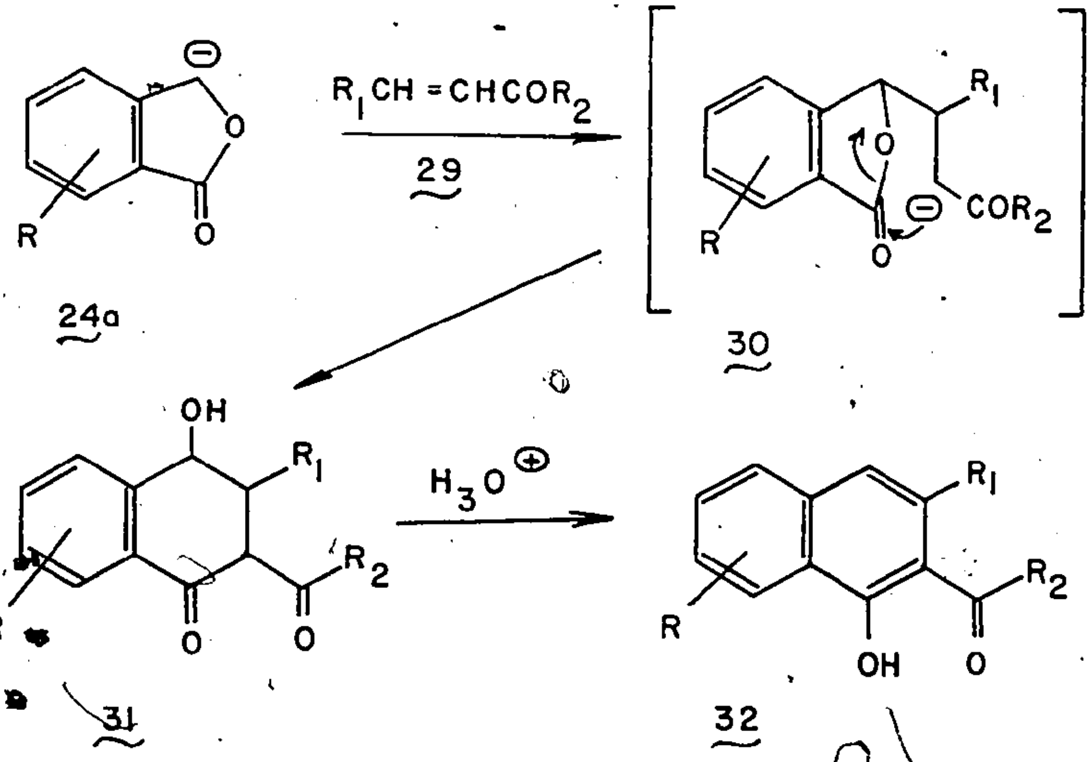
24c. X = CN

Trueb and Eugster (8) have prepared hydroxy-substituted naphthacene quinones 28 from the addition of phthalide anion 24a to substituted quinones, e.g., ethyl 8-methoxynaphthoquinone-2-carboxylate 25, to yield the adduct 26. Oxidation of 26 followed by acid catalyzed cyclization of 27 with simultaneous decarboxylation yielded 28, as shown in Scheme 5.

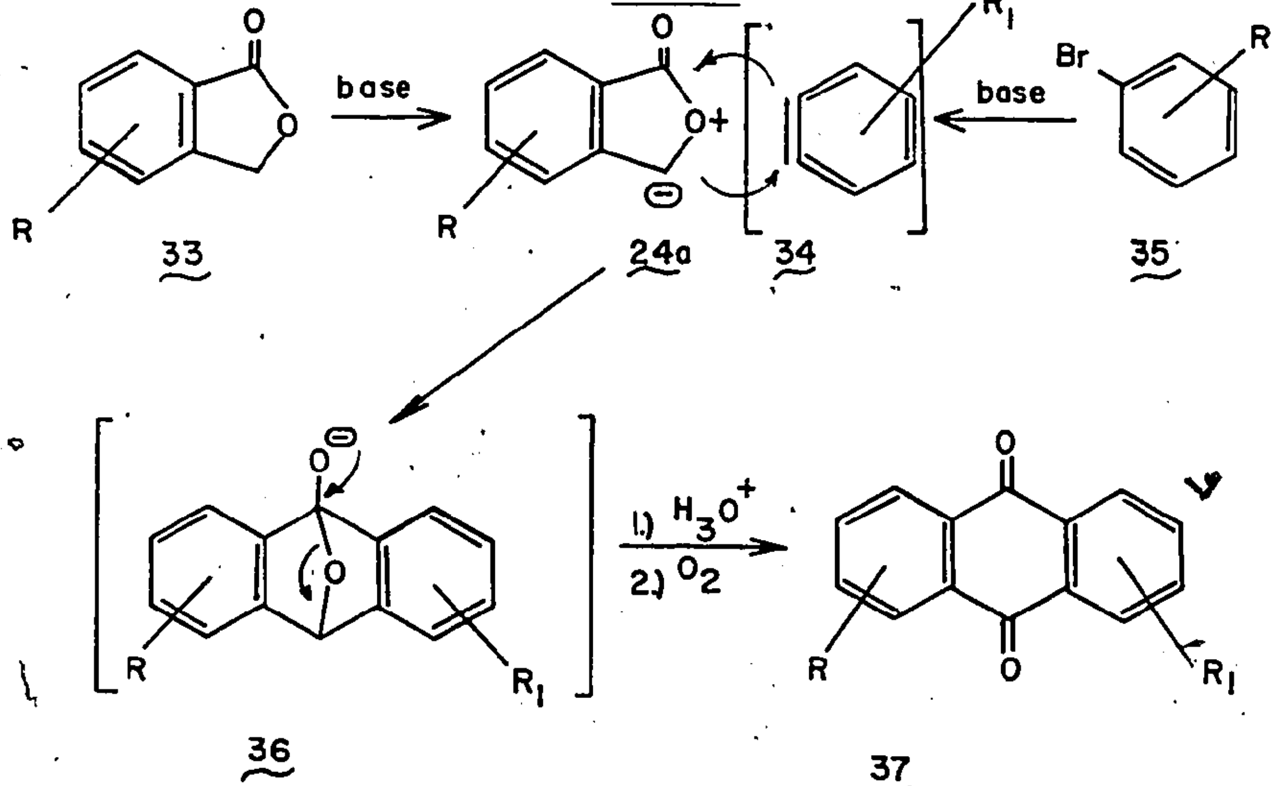


Scheme 5

Also, the group of Sammes has used the conjugate addition of phthalide anions to unsaturated ketones 29 or benzynes 34 for the preparation of naphthols 32 (9) and anthraquinones 37 (10), as shown in Schemes 6 and 7, respectively.

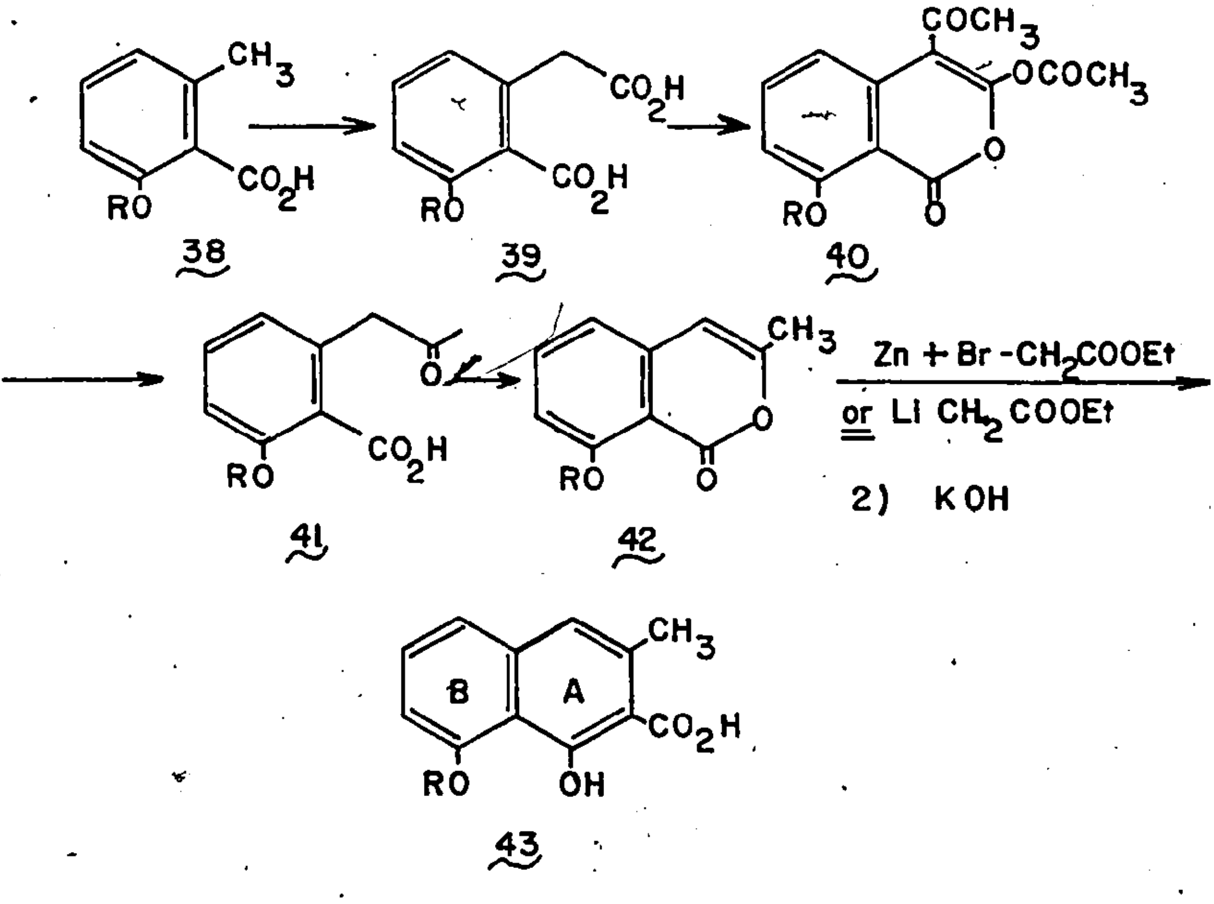


Scheme 6



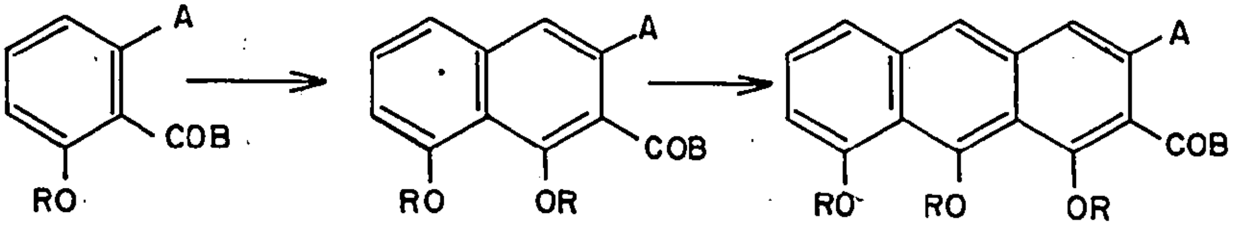
Scheme 7

Hauser and his group have developed two new methods for the regioselective annelation of aromatic rings. The first method (11) is based on construction of the isocoumarin 42. It was prepared by a three step sequence from 39 involving acylation with acetic anhydride and pyridine, basic hydrolysis with concomitant decarboxylation of 40 and, finally, ring closure of the intermediate 41 using acetic anhydride and perchloric acid. Conversion of the isocoumarin 42 to naphthoic acid 43 was accomplished by a Reformatsky reaction or by using lithium ethyl acetate (12), as shown in Scheme 8.



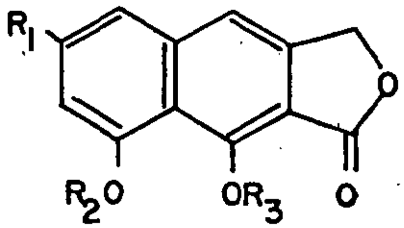
Scheme 8

Since ring A of 43 has functionality similar to 38, the reaction sequence may be repeated to add an additional ring to the system, as shown in the generalized sequence of Scheme 9.



Scheme 9

Hauser and Rhee (13) have used this method in the synthesis of sorigenin methyl ethers 44

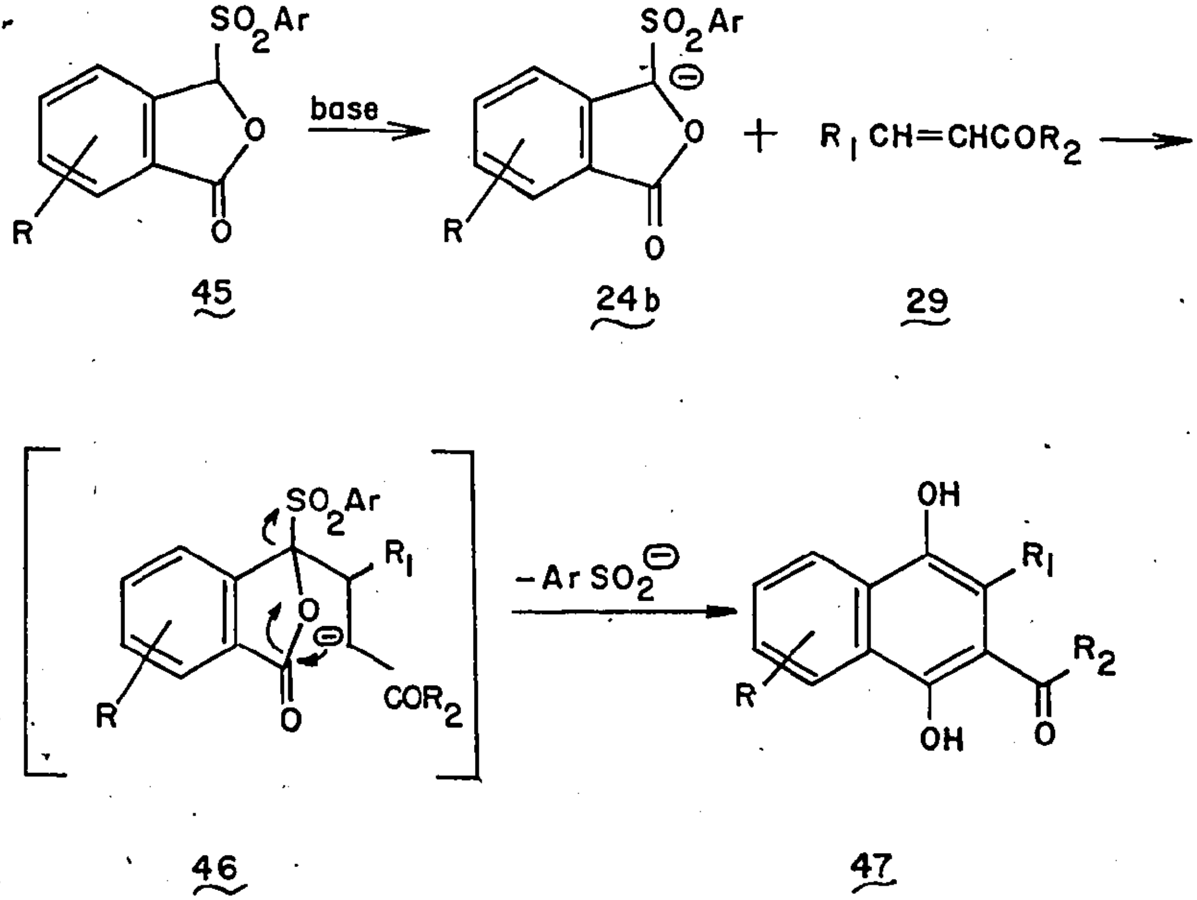


a. $R_1 = H, R_2 = R_3 = CH_3$

b. $R_1 = OCH_3; R_2 = R_3 = CH_3$

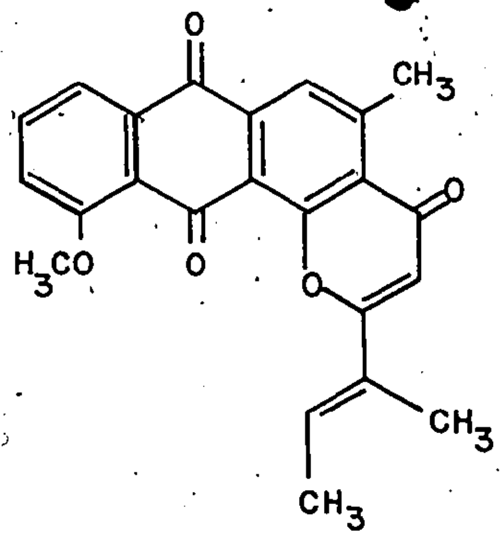
44

The second approach, used by Hauser and Rhee (14) involves nucleophilic addition of phthalide anion 24b to Michael acceptors 29. The reaction proceeds through intermediate 46 to afford directly 1, 4-dihydroxynaphthalenes 47. (Scheme 10).



Scheme 10

The same group has extended the method previously described to prepare the methyl ether of kidamycinone 48 (15a) and the tetracyclic ketone 49 (15b).



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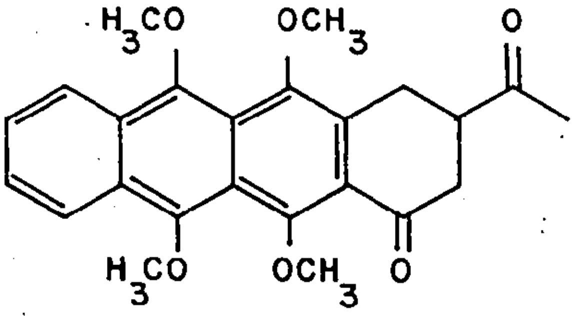
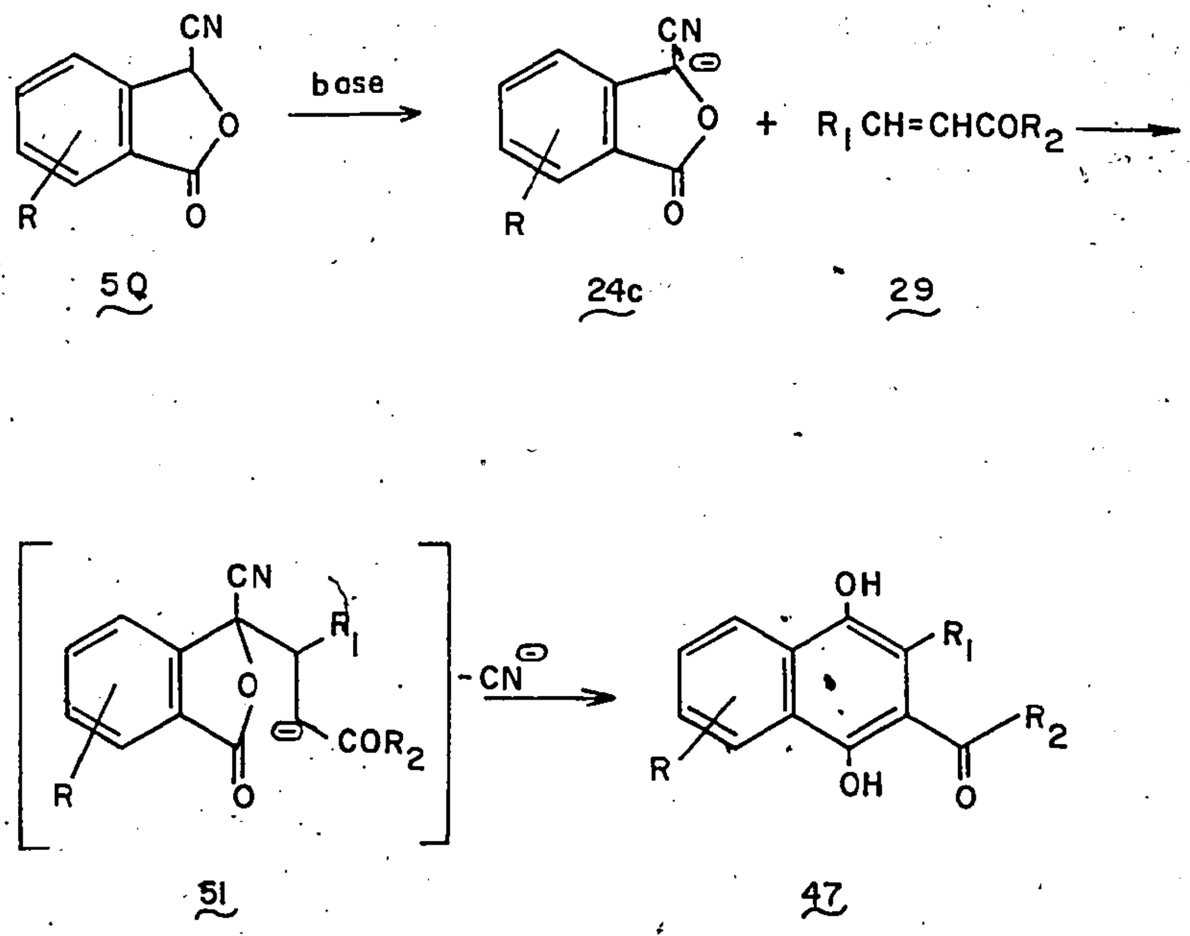


49

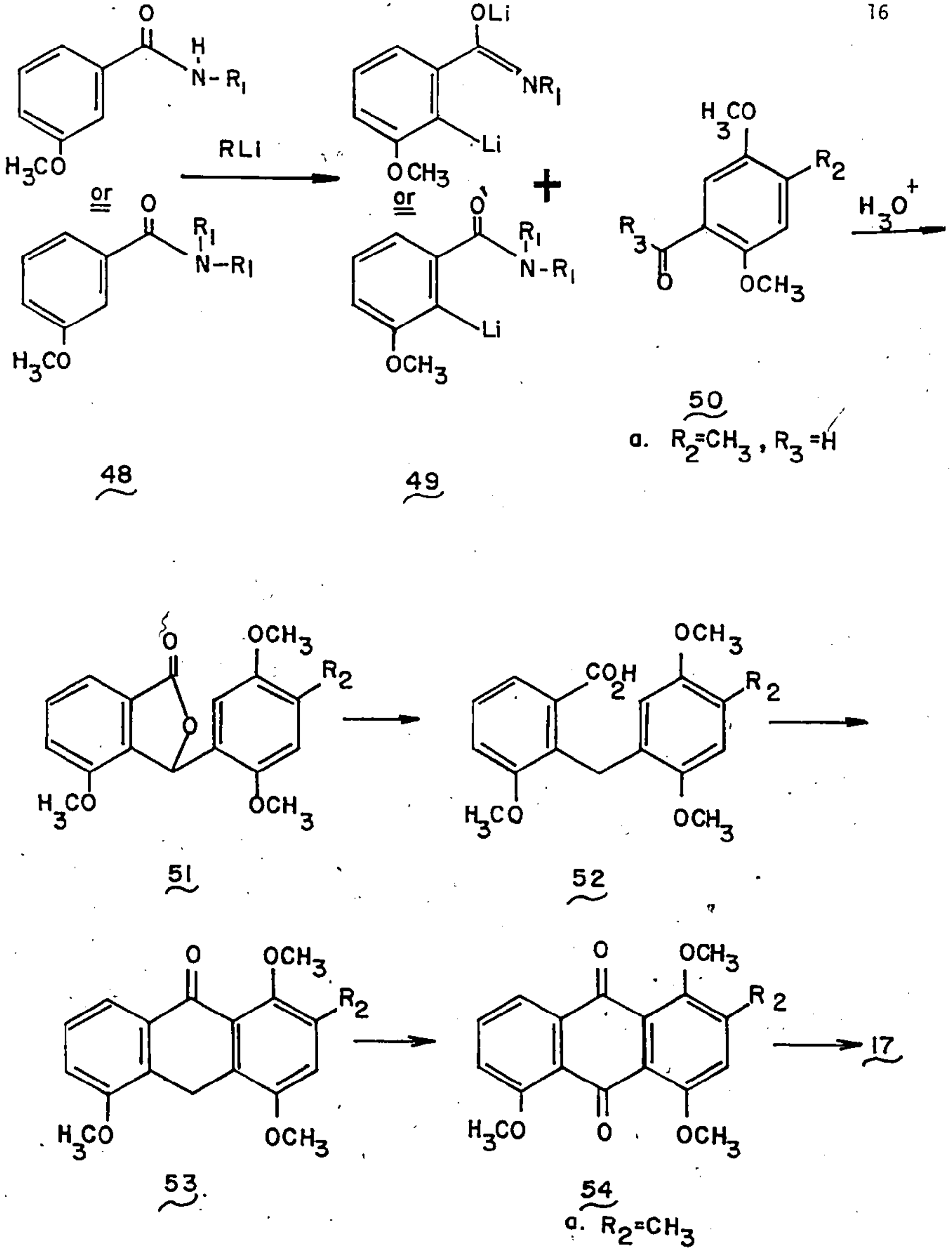
A similar ring annelation was used by Krauss and Sugimoto (16), employing addition of 3-cyanophthalide anions 24c to Michael acceptors 29 to yield 1, 4-dihydroxynaphthalenes 47, as shown in Scheme 11.



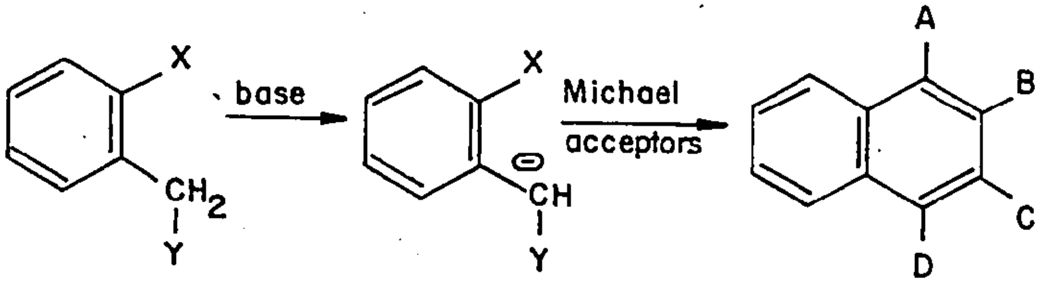
Scheme 11

Recently, Baldwin and Bair (17), Raphael et al. (18) and Snieckus et al. (19, 20) have reported syntheses of unsymmetrical anthraquinones employing organometallic coupling reactions. The method is based on the use of ortho-lithiated benzamides as key intermediates. A general sequence was used for the preparation of unsymmetrical anthraquinones, as follows: Lithiation of the amide (secondary or tertiary) 48 with an alkyl lithium (butyl or sec-butyl lithium) followed by treatment of the obtained dianion or anion 49 with an aldehyde 50 gave the 3-arylphthalide 51. Reduction of 51 afforded the o-benzylbenzoic acid derivative 52 which upon Friedel-Crafts cyclization gave the anthrone 53. Oxidation of 53 provided the corresponding anthraquinone 54 that can be converted to 17, as shown in Scheme 12. However, when an ester was used instead of the aldehyde, the condensation product with 49, after acidic work-up, was a benzoylbenzoic acid. Cyclization of the acid with H_2SO_4 yielded the anthraquinone (18).

The group of Van Leusen (21) has employed the reaction of ortho-substituted benzyl sulfone or nitrile anions 56 with Michael acceptors to obtain substituted naphthalenes 57 (Scheme 13).



SCHEME 12



55 56 57

Scheme 13

Depending on the substituents X and Y and the Michael acceptor, it is possible to obtain a variety of substituted naphthalenes, as shown in Table 1.

TABLE 1. Naphthalenes prepared from o-Substituted Benzyl Sulfones or Nitriles and Michael Acceptors.

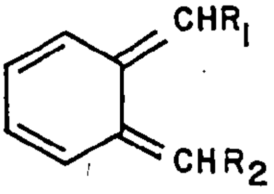
COMPOUND 57

A	B	C	D	X	Y	MICHAEL ACCEPTOR
H	COPh	Ph	H	CHO	p-$CH_3C_6H_4SO_2$	PhCH=CHCOPh
H	COOMe	Me	H	CHO	p-$CH_3C_6H_4SO_2$	CH_3CH=CHCOOMe
OH	COOEt	COOEt	H	COOEt	p-$CH_3C_6H_4SO_2$	EtOOCCH=CHCOOEt
Ph	CN	Me	H	COPh	p-$CH_3C_6H_4SO_2$	CH_3CH=CHCN
OH	COOEt	COOEt	CN	COOEt	CN	MeOOCC≡COOMe

Finally, Staunton et al. (22, 23) have reported the condensation of orsellinic acid 58 with α-Pyrones to give naphthopyrones 61 which can be converted to anthracene derivatives 62 using the Reformatsky reaction described by Hauser (11), as shown in Scheme 14. γ-Pyrones were converted to naphthalene derivatives 65, as shown in Scheme 15.

1.4 Diels-Alder Routes

The Diels-Alder reaction has also been used for the construction of polynuclear aromatic systems. One approach involves the use of o-quinodimethides 63 as reactive intermediates which readily undergo (4πs + 2πs) cycloadditions.



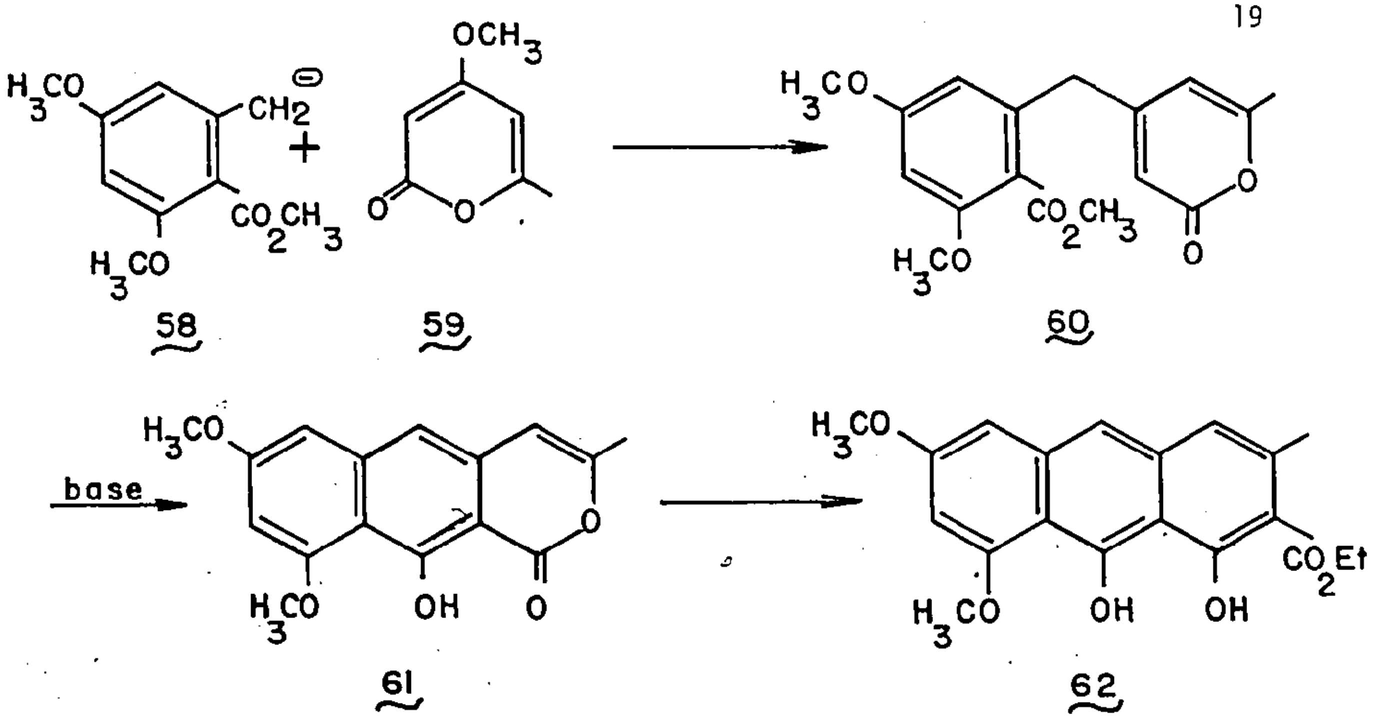
63

a. $R_1 = R_2 = H$

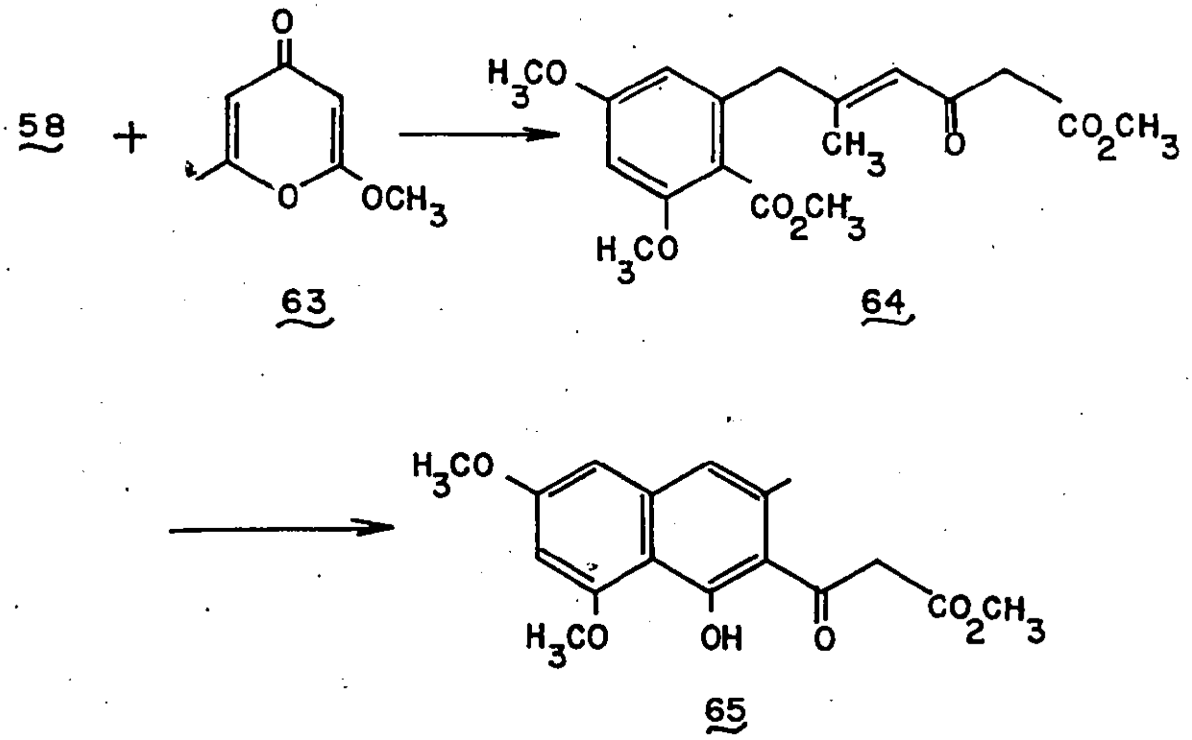
b. $R_1 = R_2 = Br$

c. $R_1 = OH$, $R_2 = H$

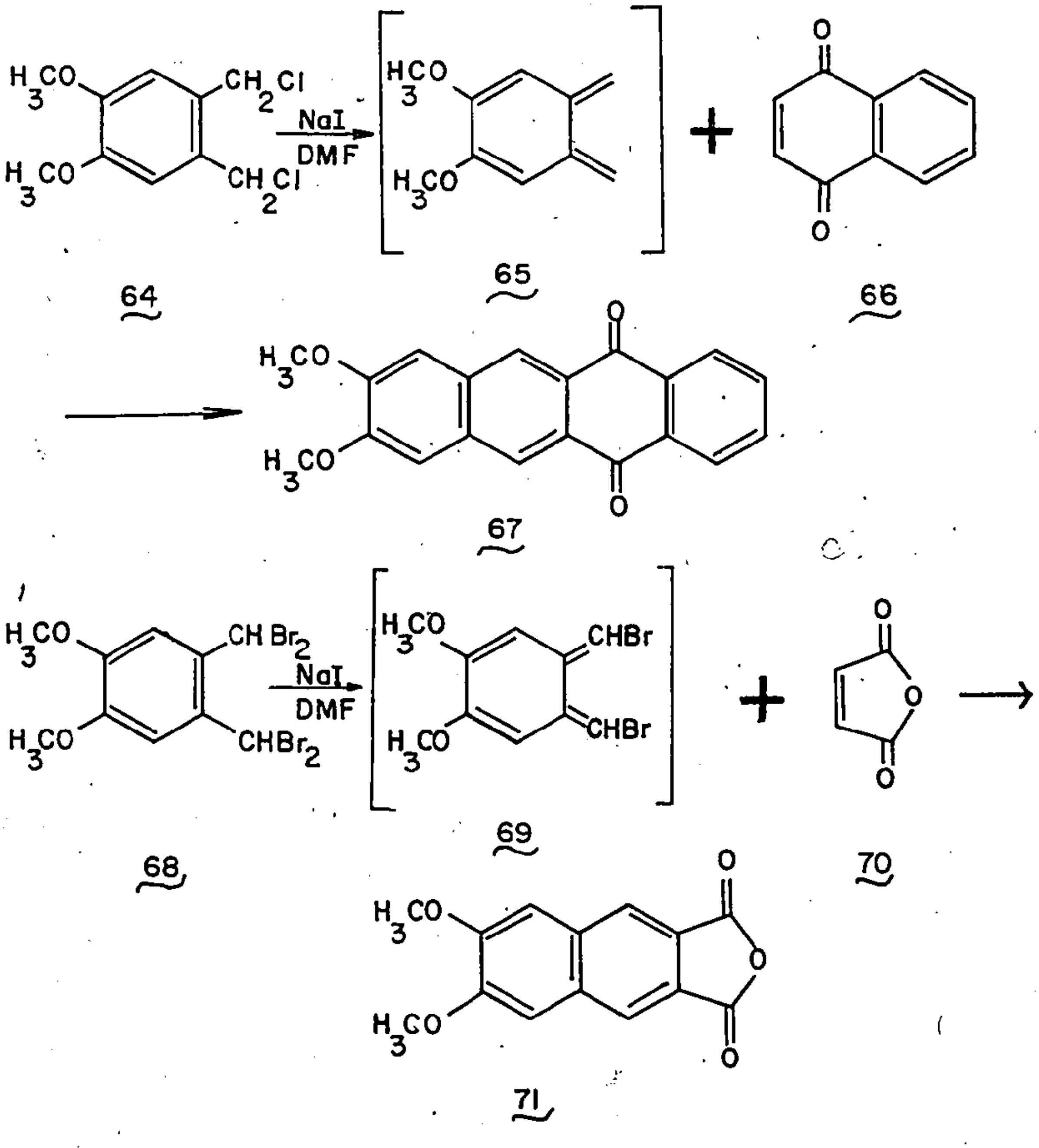
McOmie and Perry (24) have prepared some new dimethoxy derivatives of naphthalene and of polycyclic quinones using o-quinodimethides 63 as annelating agents. The intermediates 63 were generated in the presence of a dienophile by action of sodium iodide on solutions of 64 and 68, as shown in Scheme 16.



Scheme 14

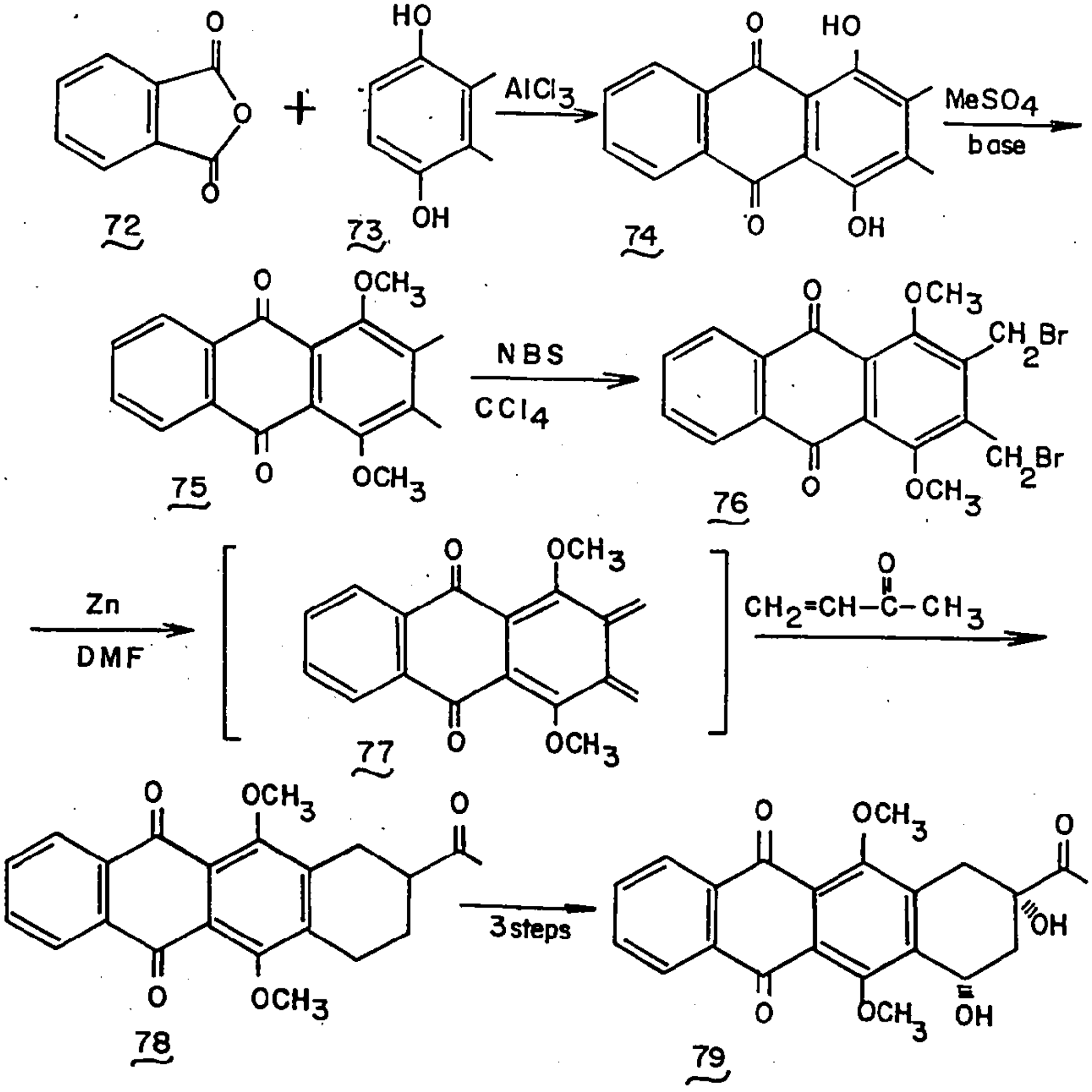


Scheme 15



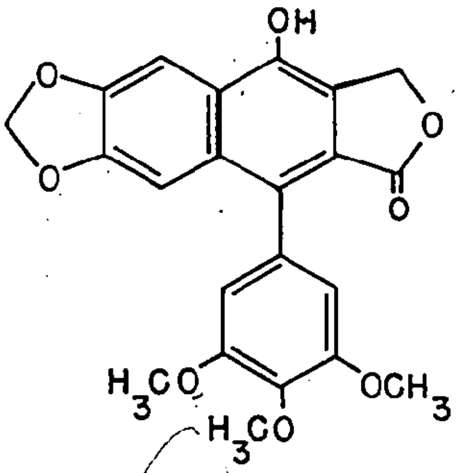
Scheme 16

In a similar way, Kerdesky and Cava (25) have prepared the anthracyclinone 79 by using the Diels-Alder addition of an o-quinodimethide intermediate 77 to methyl vinyl ketone in the key step of the synthesis of 79, as shown in Scheme 17.



Scheme 17

Sammes et al. (26, 27) have used the photoenolization process to prepare substituted naphthalenes, including members of the lignan family, such as tetradehydropodophyllotoxin 80, taiwanins E 81 and C 82 and justicidin E 83.



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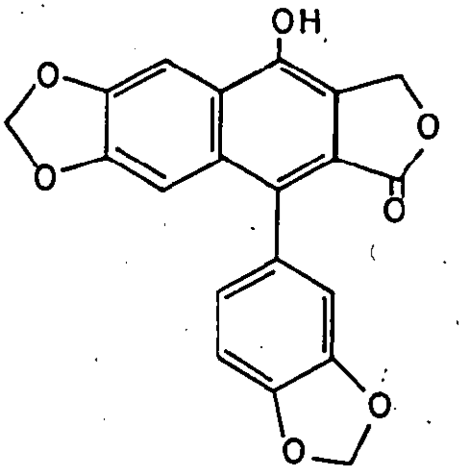

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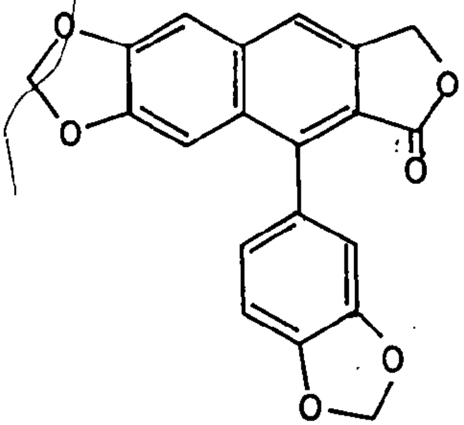
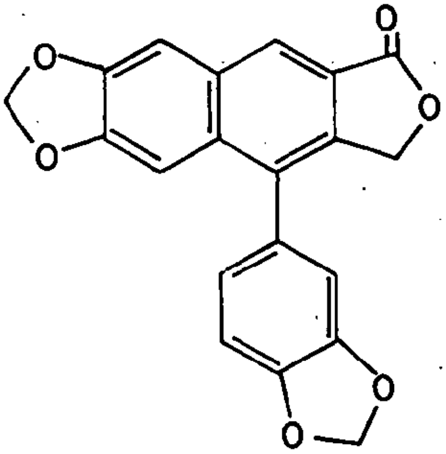
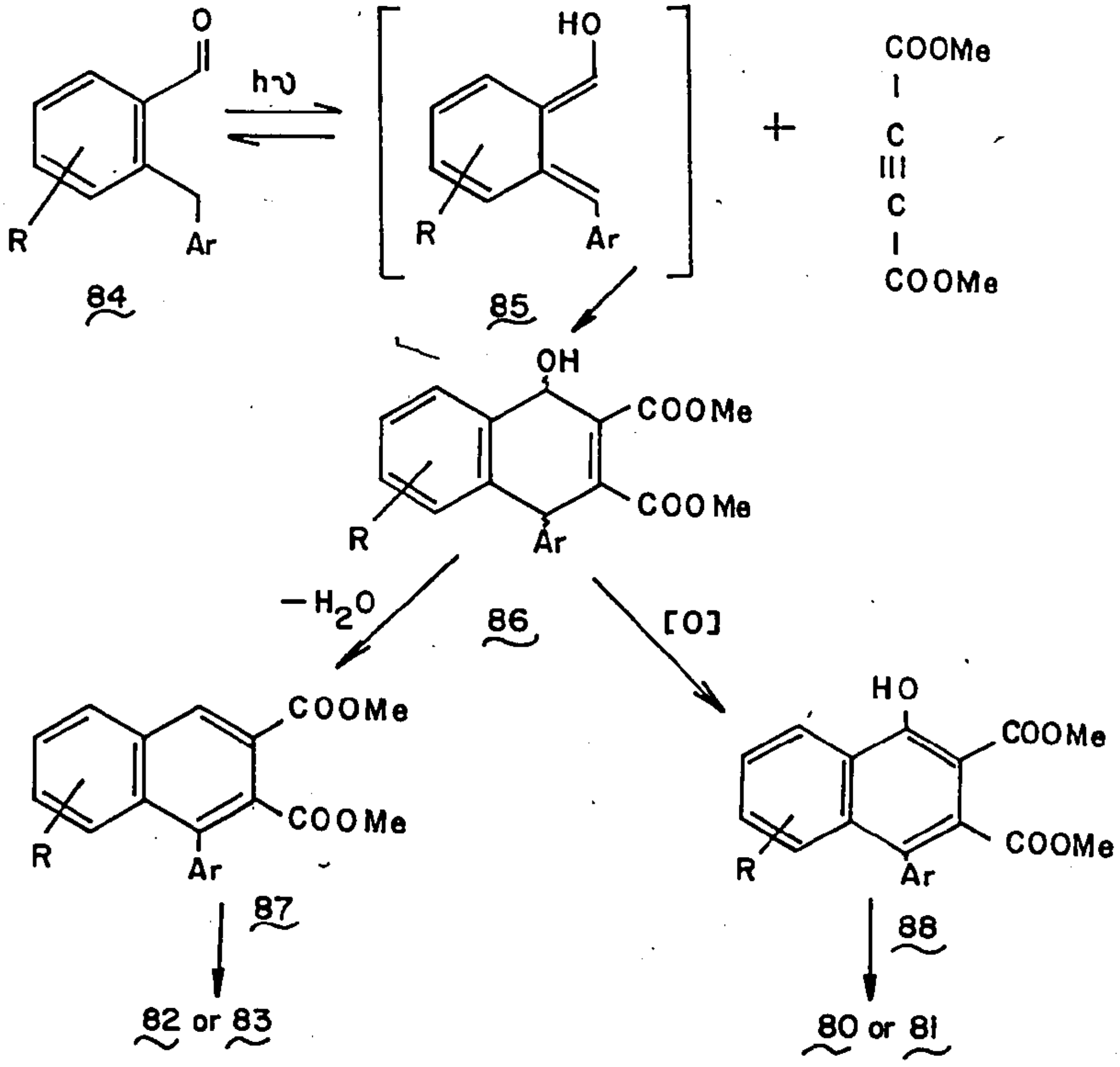


82



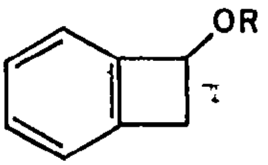
83

Thus, photolysis of ortho-substituted aromatic aldehydes generated the E-photoenol 85 which was trapped with dimethyl acetylenedicarboxylate to give an adduct 86 which could either be dehydrated to yield naphthalenes 87 or oxidized, with manganese dioxide, to yield the corresponding naphthols 88. Subsequent chemical transformations afforded the corresponding lactones, as shown in Scheme 18.



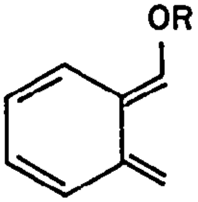
Scheme 18

Sammes et al. (28) have also used benzocyclobutenol 89a and its derivatives as a source of the enols 90a and 90b. They found that, on heating, benzocyclobutenol 89a undergoes an electrocyclic conrotatory ring opening to form the corresponding E-dienol, which may be trapped with dienophiles in the same manner as the photoenols. The enol 90a is identical with the species generated by irradiation of o-methylbenzaldehyde 91.



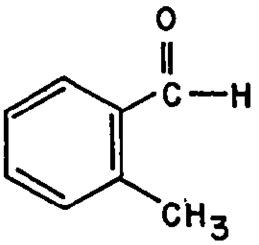
89

a. R = H
b. R = Ac



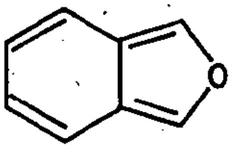
90

a. R = H
b. R = Ac



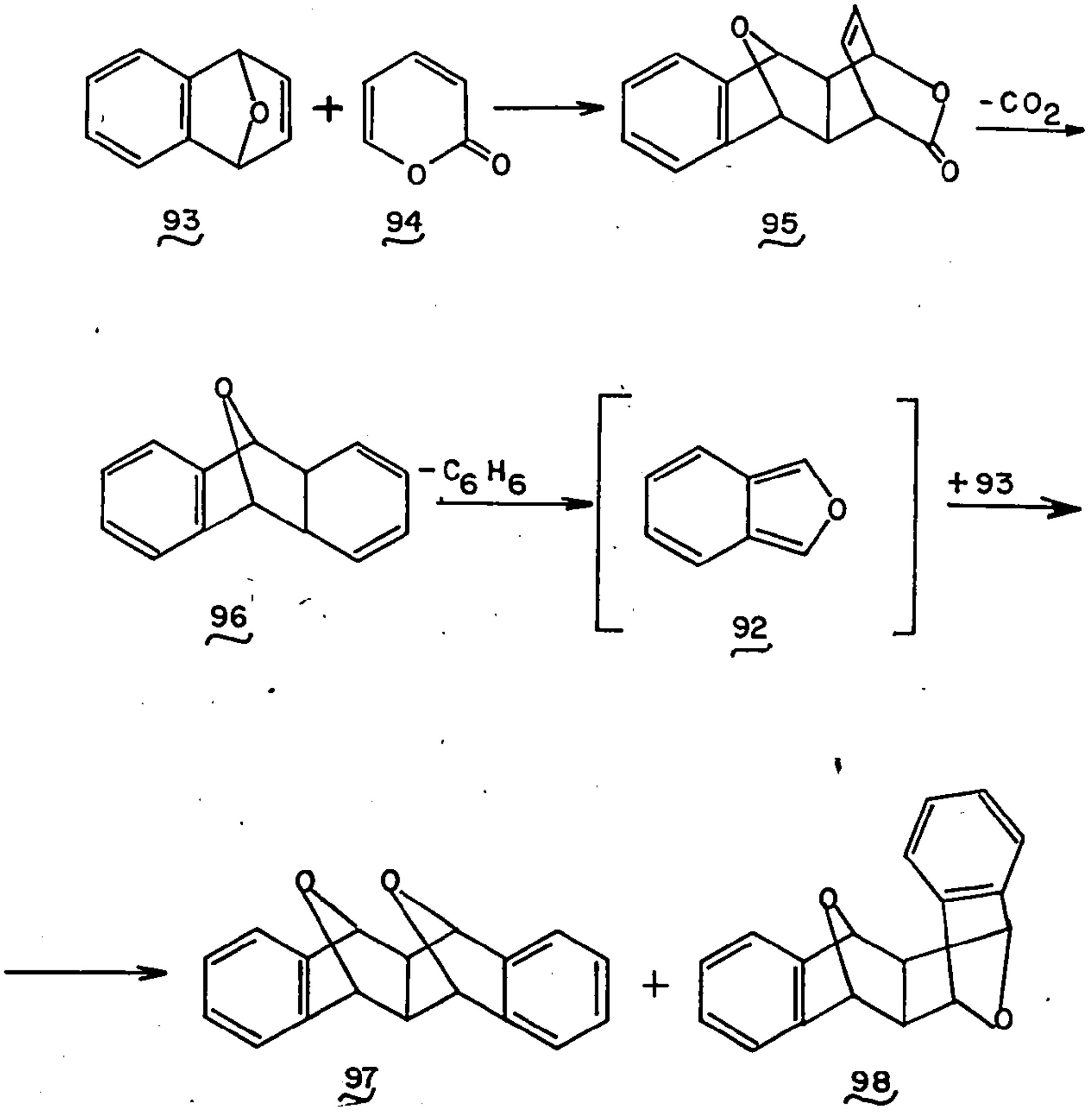
91

A second Diels-Alder approach in the synthesis of polynuclear aromatic systems, is the use of isobenzofuran 92 (29) as diene



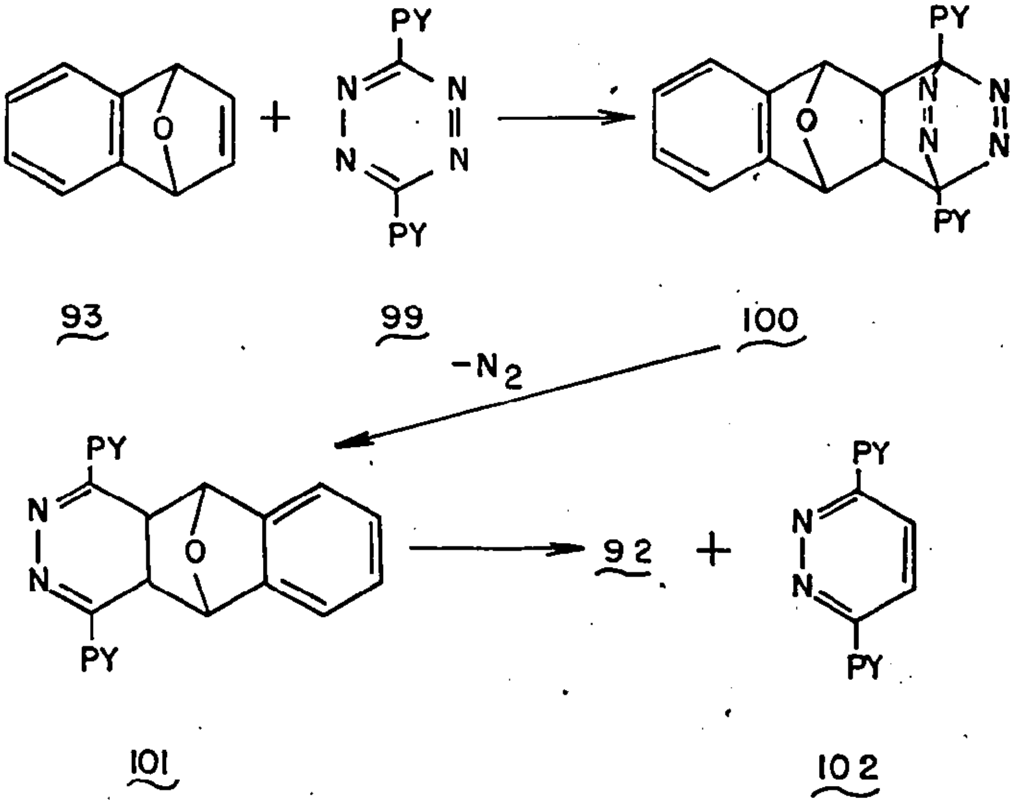
92

Isobenzofuran 92 was first postulated by Wittig (30) in 1956. Later, Fieser and Haddadin (31) trapped it as a transient intermediate in retro Diels-Alder reactions (Scheme 19).



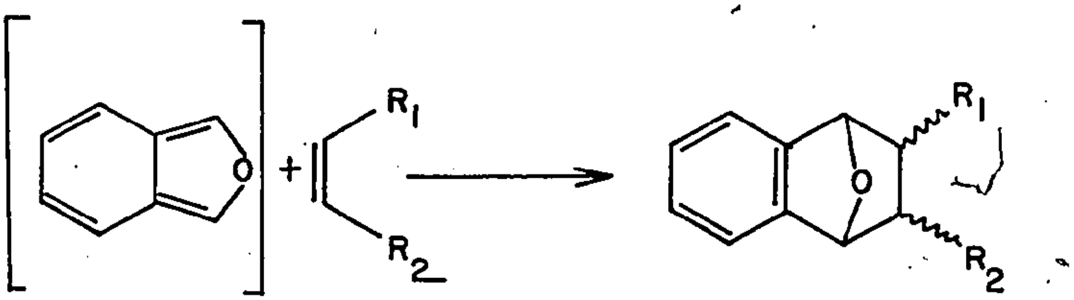
Scheme 19

Isobenzofuran 92 was isolated (32) and characterized for the first time by decomposing the adduct 100, formed from 3, 6-di-(2'-pyridyl)-s-tetrazine and 93 at 120^{0}C under reduced pressure, as shown in Scheme 20.



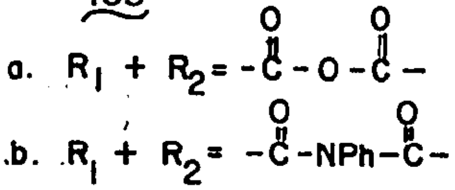
Scheme 20

Isobenzofuran 92 is a highly reactive diene; its reactivity lies in its o-quinoidal structure with the driving force of reaction being the production of a benzenoid structure. It is an excellent 4π electron substrate in 4πs + 2πs cycloaddition reactions as demonstrated by numerous Diels-Alder reactions that it undergoes. Intermediate 92 reacts instantaneously with maleic anhydride, N-phenylmaleimide and methyl vinyl ketone (33) to give adducts 103 (Scheme 21).



92

103



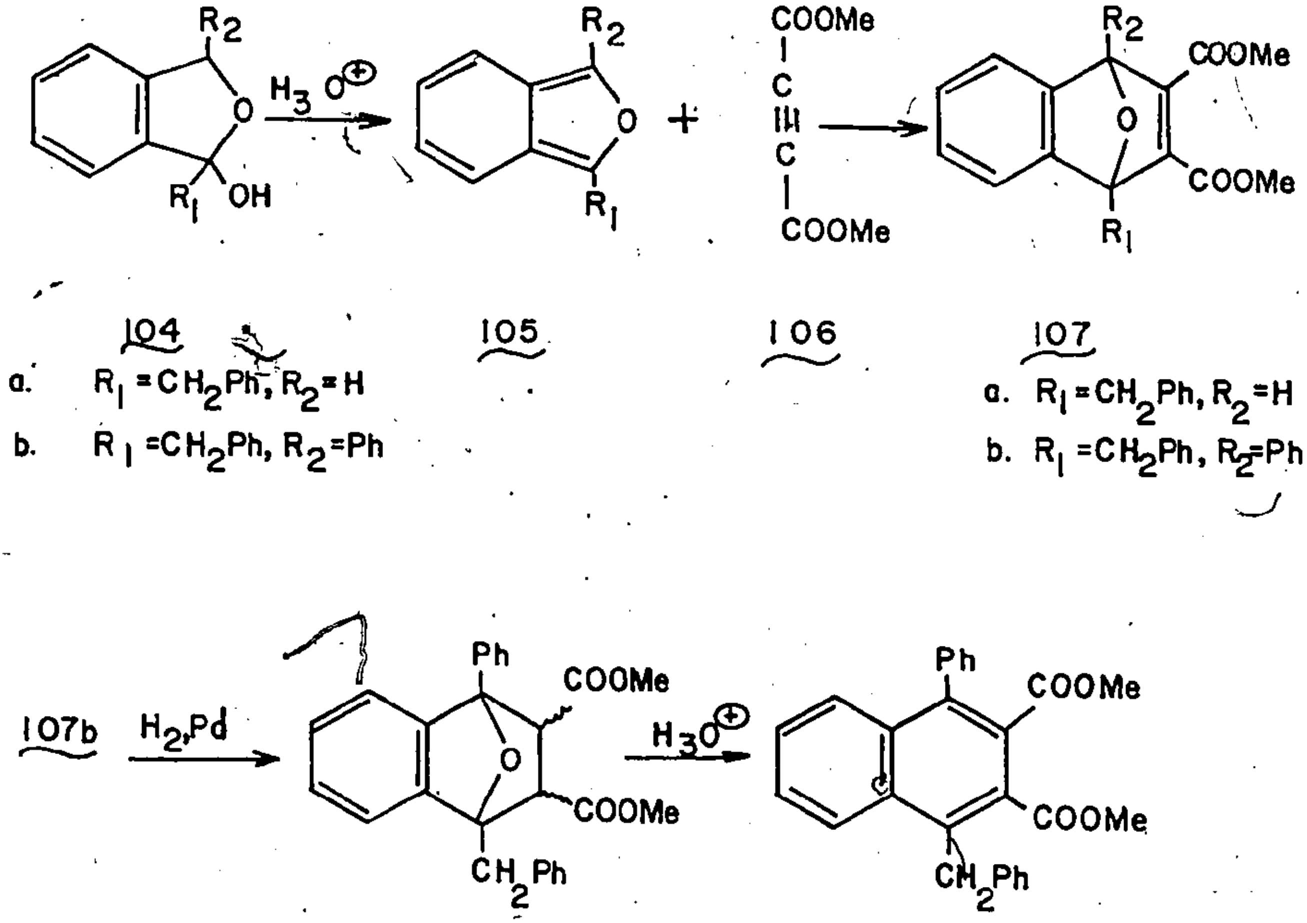
a. $R_1 + R_2 = -\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-$

b. $R_1 + R_2 = -\overset{O}{\overset{\|}{C}}-NPh-\overset{O}{\overset{\|}{C}}-$

c. $R_1 = H$, $R_2 = Ac$

Scheme 21

The Diels-Alder adducts of isobenzofurans have become useful intermediates in the preparation of derivatives of naphthalenes. Thus, Smith and Wikman (34) have prepared substituted naphthalenes and naphthols from the reaction of substituted isobenzofurans <u>105</u>, with dienophiles, e.g., dimethyl acetylenedicarboxylate <u>106</u> (Scheme 22).



104

a. $R_1 = CH_2Ph, R_2 = H$

b. $R_1 = CH_2Ph, R_2 = Ph$

105

106

107

a. $R_1 = CH_2Ph, R_2 = H$

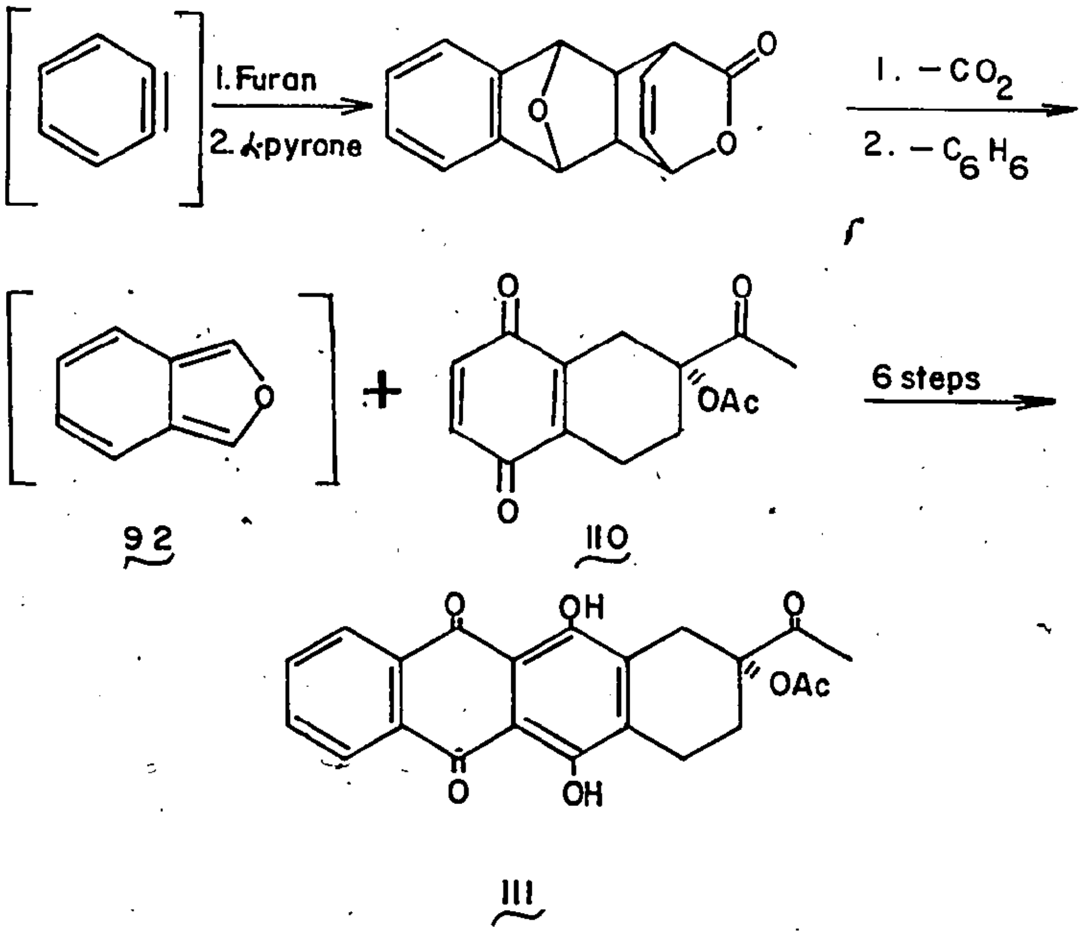
b. $R_1 = CH_2Ph, R_2 = Ph$

108

109

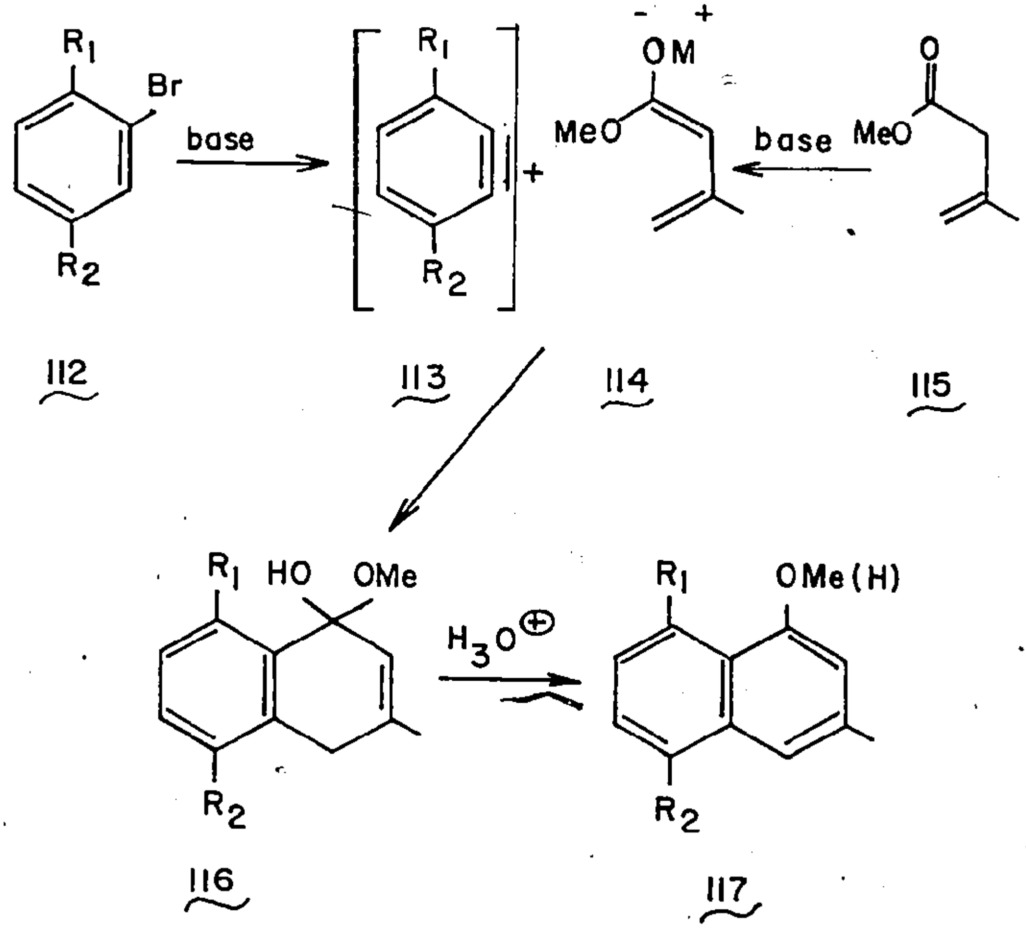
Scheme 22

Recently, Kende et al. (35) used the intermediate 92 in the synthesis of some anthracyclinones. The route involves 3 normal and 2 retro Diels-Alder reactions (Scheme 23).



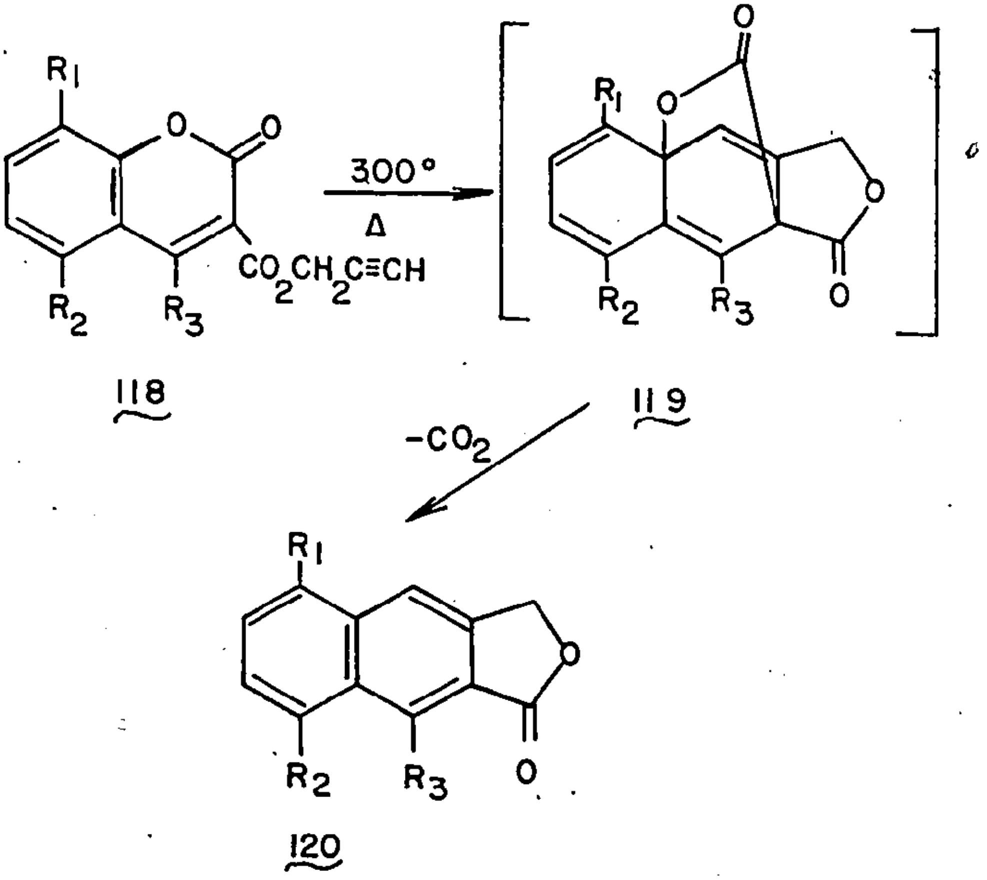
Scheme 23

Sammes and Wallace (36) have reported that dienolate anions 114 derived from α, β - unsaturated carbonyl compounds 115 undergo (4πs + 2πs) cycloaddition with benzynes 113 to give substituted naphthalenes 117 (Scheme 24).



Scheme 24

Recently, Krauss et al. (37) have reported that coumarin esters <u>118</u> undergo intramolecular Diels-Alder cycloadditions at 300°C to give the naphthoic acid lactones <u>120</u>, shown in Scheme 25.



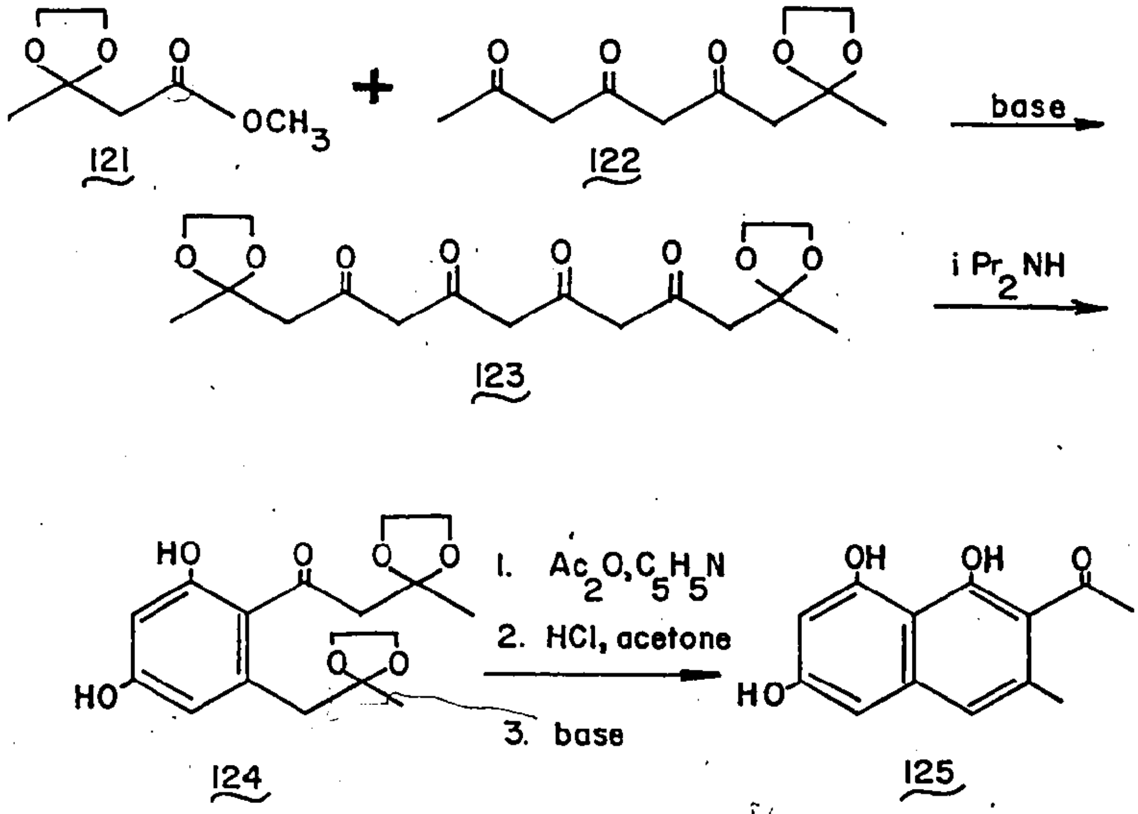
a. $R_1 = R_2 = R_3 = H$

b. $R_1 = R_2 = H$, $R_3 = OCH_3$

Scheme 25

1.5 Cyclization of Polyketides

β-Tetracarbonyl compounds have been used as intermediates in the synthesis of monocyclic aromatic natural products (38, 39). The use of higher polycarbonyl compounds as precursors in the synthesis of polynuclear aromatic natural products such as derivatives of naphthalenes or anthracenes is limited (39). Recently, however, Harris and Wittek (40) have outlined a strategy for the synthesis of naphthalenoid and anthracenoid natural products. Their method is based on the use of polyketones having the two terminal carbonyl groups protected as ketals. This method is illustrated in the synthesis of 6-hydroxymusizin 125 (Scheme 26).



Scheme 26

This review has shown that there is great current interest in the development of methods for the synthesis of polycyclic aromatic and hydroaromatic systems. Much of this interest is associated with the recognition of biological activity in many compounds of these structural types. The work reported in this thesis describes a new synthetic method that also shows promise for the synthesis of such systems. As the subsequent chapter will show, this method uses phthalides as starting materials as did many of the methods described in this review. However, the approach used here is significantly different from that of other works as the subsequent chapter will reveal.

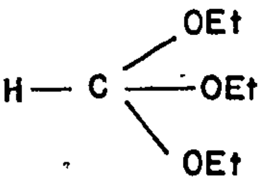
CHAPTER 2

RESULTS AND DISCUSSION

2.1 Introduction

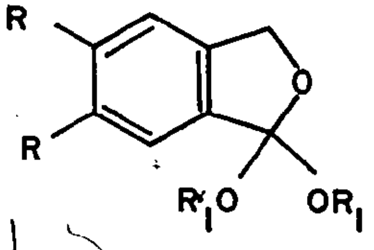
The various approaches to the synthesis of functionalized naphthalenes have been described. Some of these methods involve the use of phthalides (8, 10, 11, 14, 16) as intermediates, as does this work in which ortho esters of phthalide are used.

Ortho esters of carboxylic acids (41, 42) are substances having a carbon atom linked by oxygen bridges to three other carbon atoms. They include acylic ortho esters 126, as well as a variety of heterocyclic substances such as the lactone acetals, e.g., 1,1-dialkoxyphthalans 127. Ortho esters are reagents widely used in organic synthesis, and some of the cyclic ortho esters are useful intermediates for the protection of hydroxy and carboxylic acid groups during multistep syntheses.



$\mathrm{H{-}C(OEt)_3}$

126



127

a. $R = R = H$, $R_1 = R_1 = C_2H_5$

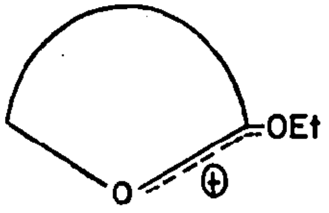
b. $R = R = OCH_3$, $R_1 = R_1 = C_2H_5$

c. $R = R = H$, $R_1 = R_1 = OCH_3$

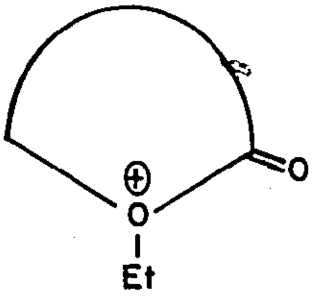
When this study was begun, the use of phthalide ortho esters 127 as synthetic intermediates in natural products synthesis or for the construction of other organic molecules of special interest, had not been reported.

2.2 Synthesis of Phthalide Ortho Esters

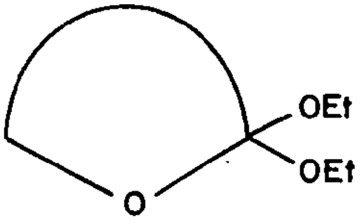
It is known that trialkyloxonium fluoroborates alkylate lactones only at the carbonyl oxygen (43). The explanation of such selectivity is that the resulting cation 128 is stabilized by resonance, unlike the cation 129 which would be obtained by alkylation at the cyclic oxygen atom.



128



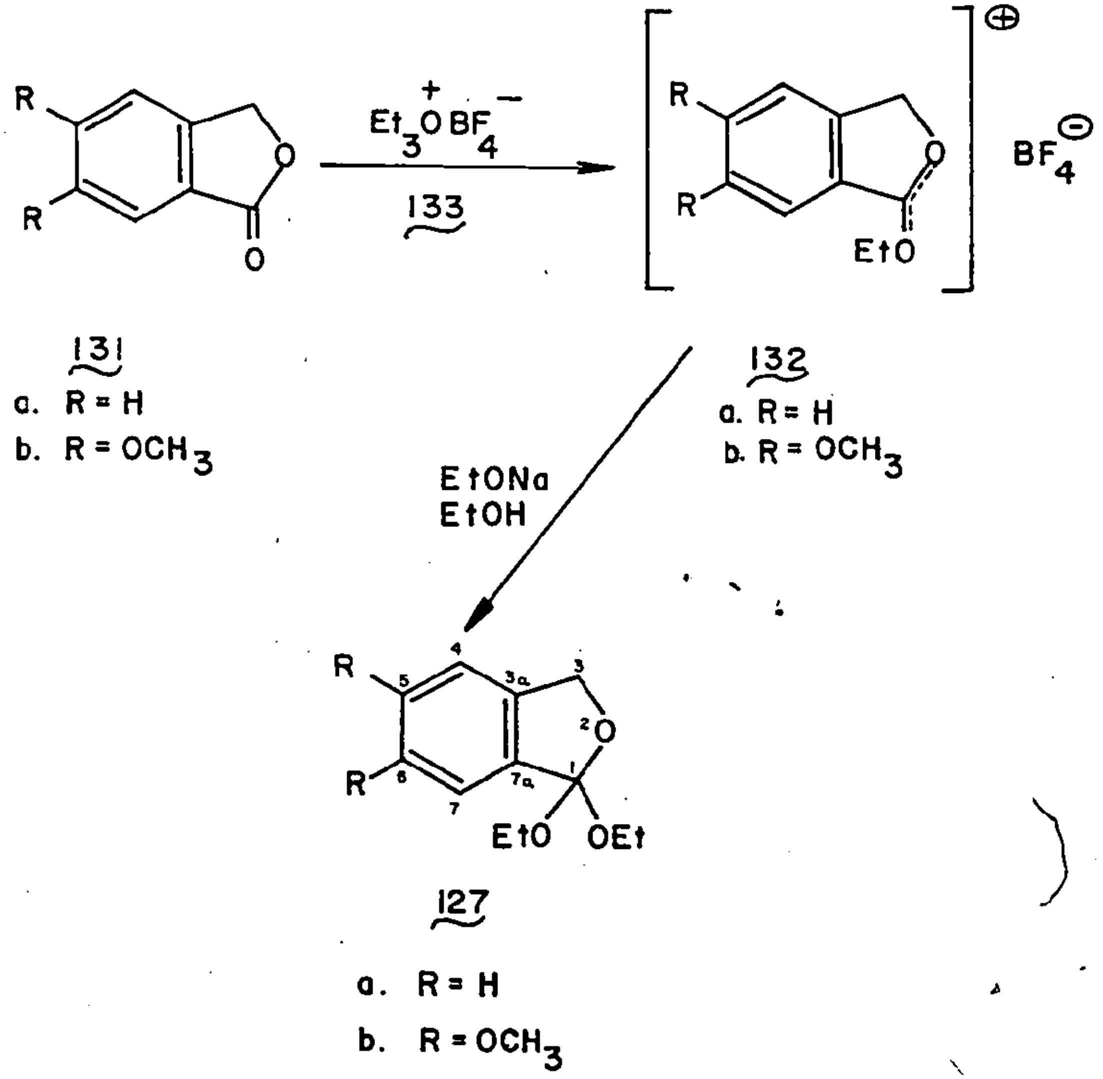
129



130

Treatment of salts such as 128 with sodium ethoxide converts them into ortho esters.

1,1-diethoxyphthalan 127a (43) has been prepared by the alkylation of phthalide 131a with triethyloxonium fluoroborate 133 (44) followed by treatment of the obtained fluoroborate salt 132a with sodium ethoxide in ethanol at room temperature, as demonstrated in Scheme 27.


R
R
O
O
$Et_3\overset{+}{O}BF_4^-$
133
R
R
O
EtO
⊕
$BF_4^{\ominus}$
131
a. R = H
b. R = OCH3
132
a. R = H
b. R = OCH3
EtONa
EtOH
R
R
4
5
6
7
3a
7a
3
2
O
1
EtO
OEt
127
a. R = H
b. R = OCH3

Scheme 27

5,6-dimethoxy-1,1-diethoxyphthalan 127b was prepared in a similar manner to 127a, but without isolation of the fluoroborate salt 132b. The addition of sodium ethoxide was carried out at -30°C according to Deslongchamps' procedure (45).

The structures of 127a and 127b are based on their method of preparation and on their spectral properties. In the ^1H NMR spectrum of 127a (Figure 1) the two methyl groups have the same chemical shift and appear as a triplet centered at 1.17 δ. The methylene quartets, however, appear as overlapping signals in the range 3.2 - 3.9 δ. The singlet at 5.07 δ has been assigned to the protons at C-3. The signals of the aromatic protons appear as a multiplet at 7.2 - 7.6 δ.

The ^1H NMR spectrum of 127b (Figure 2) reflects the structural difference between it and 127a. The methoxy groups appear as a singlet at 3.92 δ and the two aromatic protons as singlets at 6.77 and 6.95 δ. Otherwise, the spectra are similar.

The ^{13}C NMR spectrum* of 127a (Table 2) showed only three resonances in the aliphatic region. They arise from the methyl and methylene carbon atoms of the ethyl group and appear at 15.2 and 58.8 ppm, respectively. The signal of the benzylic carbon atom at C-3 is at 70.7 ppm. These chemical shifts fall in the same order as those reported for the corresponding carbon atoms of 134 (45). The signal

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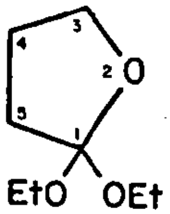
* ^{13}C NMR spectra reported in this thesis were recorded by Dr. D. W. Hughes formerly of this laboratory. Dr. Hughes also provided much assistance in the interpretation of the spectra.

TABLE 2. ^{13}C NMR chemical shifts of phthalides and ortho esters

Carbon	131a	131b	127a	127b	134
1	170.4	171.4	123.9	124.5	118.4
3	69.5	69.2	70.7	70.9	63.6
3a	146.3	141.3	140.1	132.2	
4	122.0	103.8	122.8^{a}	105.0^{a}	28.1
5	133.6	155.2	129.6^{b}	151.2^{b}	30.4
6	128.5	150.7	127.9^{b}	149.9^{b}	
7	124.9	106.4	121.2^{a}	103.6^{a}	
7a	125.2	117.8	135.7	127.3	
1-O$\underline{\mathrm{CH_2}}CH_3$			58.8	58.8	57.0
1-OCH$_2\underline{\mathrm{CH_3}}$			15.2	15.3	15.2
5-OCH$_3$		56.4		56.0	
6-OCH$_3$		56.4		56.0	

a, b These assignments may be reversed.

at 123.9 ppm was assigned to the carbon at C-1 because of its quaternary character and in analogy with the corresponding carbon atom of 134. The two other quaternary C-atoms are assigned to 3a and 7a in analogy with the spectrum of phthalide 131a. The protonated aromatic carbons cannot be assigned definitively without further studies.

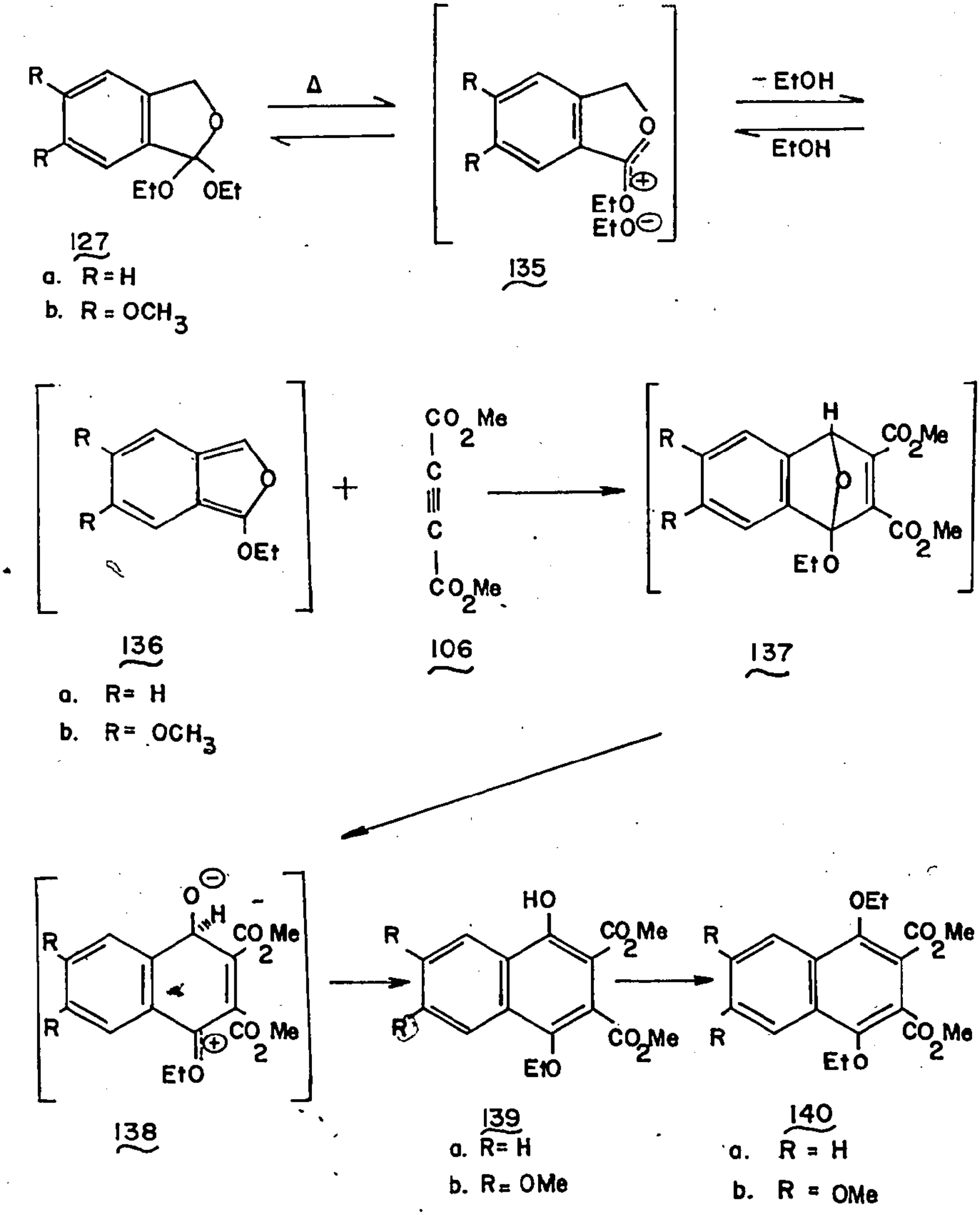


134

The ^{13}C NMR spectrum of 127b (Table 2) showed that the signals of the ethyl carbon atoms, the benzylic carbon atom at C-3, and the carbon atom of the ortho ester function are nearly identical with those in 127a. The additional signal from the carbon atoms of the methoxy groups occurs at 56.0 ppm. These assignments were confirmed by the off-resonance spectrum. The assignment of the aromatic carbon atoms in 127b was based on the application of the substituent parameters derived for ortho dimethoxy groups to the spectrum of 127a (46).

2.3 Reaction of 127a and 127b with Dimethyl Acetylenedicarboxylate

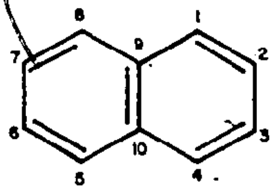
Treatment of 127a and 127b with dimethyl acetylenedicarboxylate 106 in a sealed glass tube or at atmospheric pressure, in each case, at a temperature of 140-150°C, for 6 h gave the naphthalene derivatives 139a and 139b (Scheme 28) in yields of 60 - 75%. From both systems, a single compound was isolated. The structures of 139a


R
R
EtO
OEt
127
a. R = H
b. R = OCH3
Δ
R
R
O
EtO
EtO
135
− EtOH
EtOH
R
R
O
OEt
136
a. R = H
b. R = OCH3
+
CO2Me
C
C
CO2Me
106
H
CO2Me
CO2Me
EtO
137
O
H
CO2Me
CO2Me
EtO
138
HO
CO2Me
CO2Me
EtO
139
a. R = H
b. R = OMe
OEt
CO2Me
CO2Me
EtO
140
a. R = H
b. R = OMe

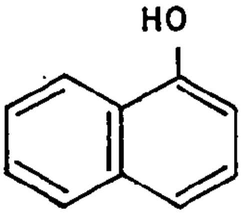
Scheme 28

and 139b are based on their elemental analyses and their spectroscopic properties. The infrared spectrum of each product, 139 and 139b, showed two bands in the carbonyl region at 1735 and 1670 cm^{-1} attributed to ester absorption. The lower field absorption is attributed to an intramolecularly hydrogen-bonded ester carbonyl group (47). The hydroxyl absorption resulting from intramolecular hydrogen bonding was not clearly visible as it underlay and was obscured by the C-H absorption. The ^{1}H NMR spectra of 139a (Figure 3) and 139b (Figure 5) both showed a peak at 12.1 δ for a hydrogen-bonded hydroxyl proton (48), as well as other peaks consistent with the assigned structures. Ethylation of 139a and 139b with ethyl iodide and sodium hydride in tetrahydrofuran (THF) (49) gave the symmetrical compounds 140a and 140b (Scheme 28), each in 60% yield. The infrared spectrum of 140a and 140b showed only one absorption attributed to the ester carbonyl group (1735 cm^{-1}). The ^{1}H NMR spectrum of 140a (Figure 4) showed four aromatic protons forming an AA' BB' pattern with two multiplets centered at 7.65 and 8.22 δ. The other signals in the spectrum are in accord with the proposed structure. The ^{1}H NMR spectrum of 140b (Figure 6) showed a singlet of area 2 attributed to aromatic protons at 7.46 δ, and signals attributed to methoxy groups on the aromatic ring and of the ester group at 3.98 and 4.03 δ each of area 6. Signals attributed to the ethyl groups appear at 1.48 (t) and 4.18 (q) δ associated with the methyl and methylene groups, respectively.

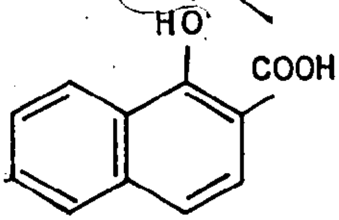
The ^{13}C NMR spectra of 139a, 139b, 140a, and 140b are recorded in tabular form (Appendix, Table 3). The chemical shifts are in agreement with the structures proposed for the substituted naphthalenes. However, the assignments of the aromatic carbon atoms are tentative. The assignment of chemical shifts to individual carbon atoms was made by D. W. Hughes (50) by comparison to the published spectra of naphthalene 141 (51, 52) and 1-naphthol 142 (51, 52) and by examination of the model compounds, 1-hydroxy-2-naphthoic acid 143 and naphthalene-2,3-dicarboxylic acid 144, and its dimethyl ester 145 (Appendix, Table 4).



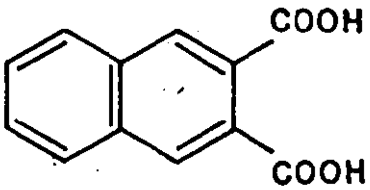
141



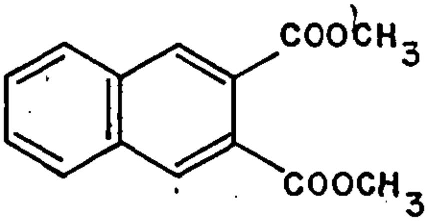
142



143



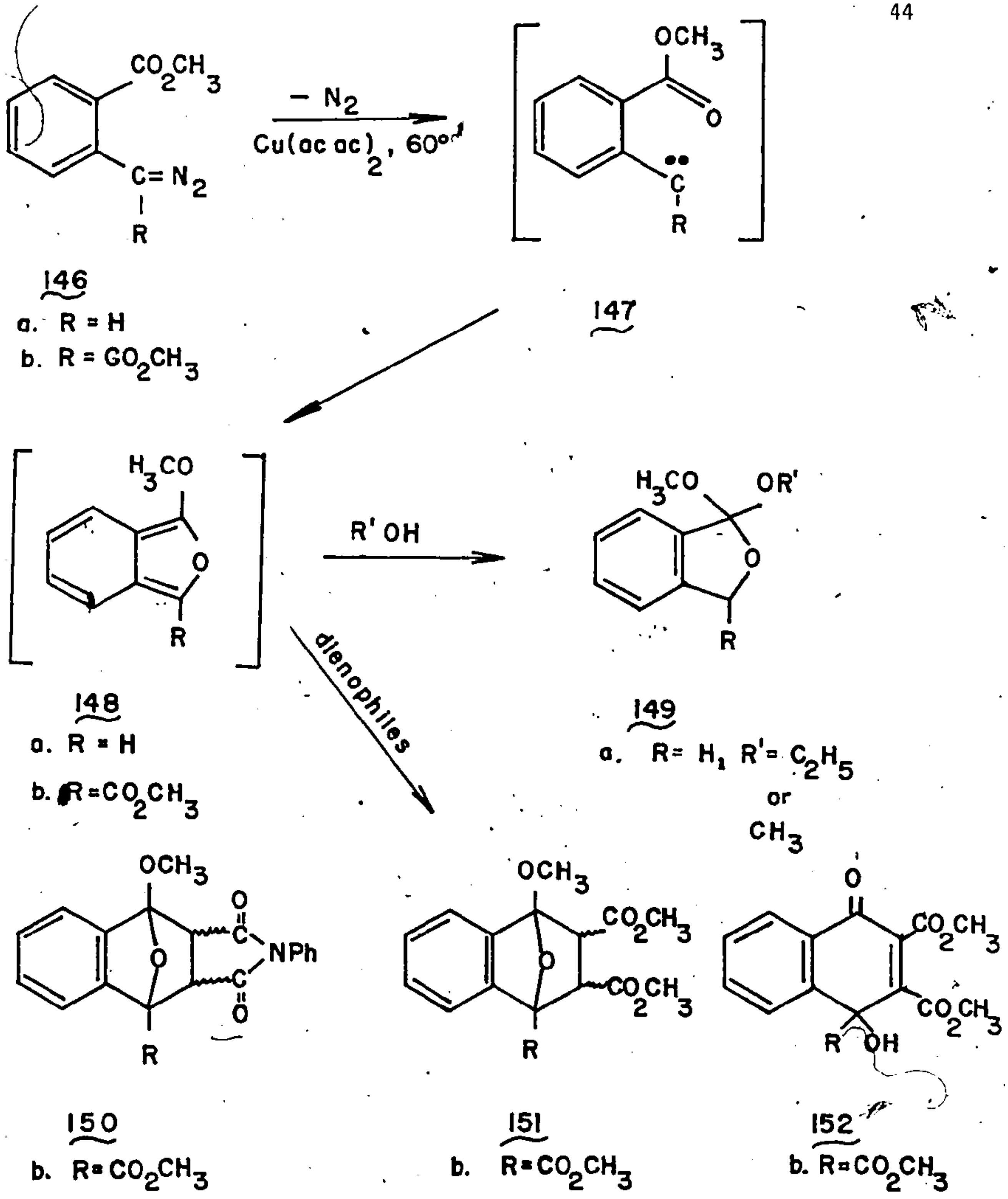
144



145

A significant feature of these data, in a structural sense, is that it is possible to differentiate a hydrogen-bonded carbonyl carbon absorption in an ester from a non-bonded ester absorption. For example, the carbonyl carbon on C-2 in 139a and 139b is deshielded by 2 ppm with respect to the carbonyl carbon on C-3. Another feature is that the C-2 carbon in 139a and 139b usually appears as the highest field absorption in the aromatic region because of the mesomeric effect of the OH group at C-1.

The formation of 139a and 139b can be rationalized as shown in Scheme 28. The reaction is considered to take place through the formation of a transient 1-ethoxyisobenzofuran intermediate 136, generated in situ, which readily undergoes cycloaddition ($4\pi s + 2\pi s$) with 106 to yield the tricyclic intermediate 137. It is proposed that the intermediate 137 undergoes C-O bond cleavage to 138 at the elevated temperature of the reaction and that the latter collapses to 139. There is not direct evidence for the generation of the intermediates 136, 137 or 138. However, Hamaguchi and Ibata (53) have proposed the presence of an intermediate similar to 136. They found that methyl o-diazomethylbenzoates 146 decomposed in the presence of $Cu(acac)_2$ to give 1-methoxyisobenzofurans 148. These intermediates are considered to form by interaction between a carbene, formed by decomposition of the diazo group, and the carbonyl group. The intermediates were trapped with alcohol (methanol or ethanol) or dienophiles such as N-phenylmaleimide, dimethyl fumarate and dimethyl acetylenedicarboxylate to give phthalide ortho esters 149 and Diels-



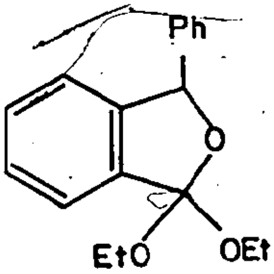
CO2CH3
C=N2
R
146
a. R = H
b. R = CO2CH3
− N2
Cu(acac)2, 60°
OCH3
O
C
R
147
H3CO
O
R
148
a. R = H
b. R = CO2CH3
R'OH
H3CO
OR'
O
R
149
a. R = H, R' = C2H5 or CH3
dienophiles
OCH3
O
NPh
R
150
b. R = CO2CH3
OCH3
CO2CH3
CO2CH3
R
151
b. R = CO2CH3
O
CO2CH3
CO2CH3
R OH
152
b. R = CO2CH3

Scheme 29

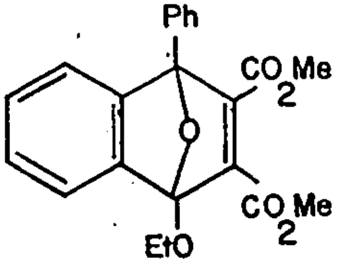
Alder adducts 150b, 151b and 152b, respectively, (Scheme 29).

In order to test the proposed mechanism for the formation of compounds 139a and 139b, a series of experiments was carried out.

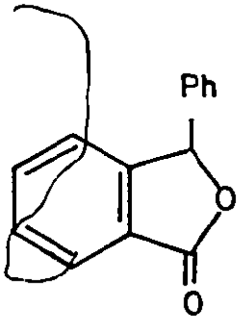
An attempt was made to prepare 3-phenyl-1,1-diethoxyphthalan 153 and use it as a substrate for the Diels-Alder reaction with 106. The final product was expected to be the tricyclic intermediate 154 because it could not collapse to a naphthalene. Several attempts using conventional methods were made to prepare 153 from 3-phenylphthalide 155 without success.



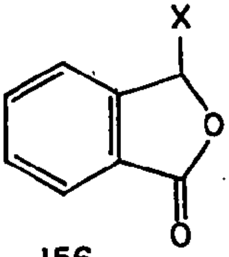
153



154



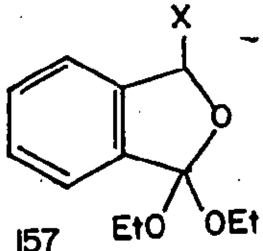
155



156

a. X = Cl

b. X = Br

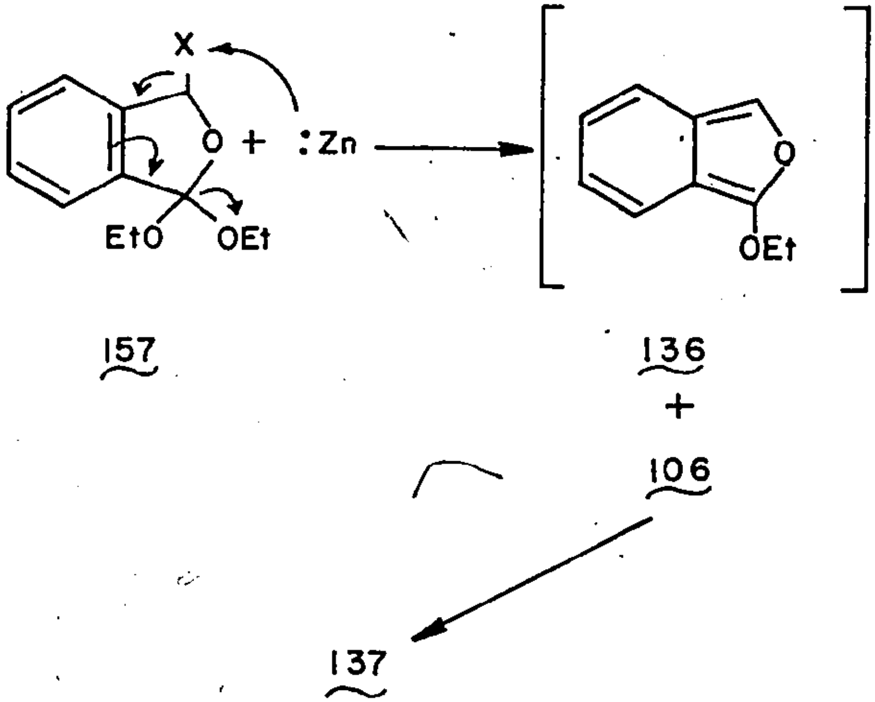


157

a. X = Cl

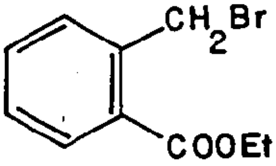
b. X = Br

In another approach, an attempt was made to prepare 3-chloro or 3-bromo-1,1-diethoxyphthalans 157 with the intention to study their reaction with metals such as Zn or Mg to generate the intermediate 136 (Scheme 30). However, the alkylation of 3-chloro or 3-bromophthalide 156 with triethyloxonium fluoroborate 133 failed.

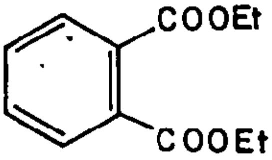


Scheme 30

Direct halogenation of 127a was then attempted. Bromination with N-bromosuccinimide in carbon tetrachloride yielded a mixture of two compounds tentatively identified from the mass spectrum of the mixture as o-ethoxycarbonylbenzyl bromide 158 and the diethyl ester of phthalic acid 159. However, the desired compound 157b was not obtained.

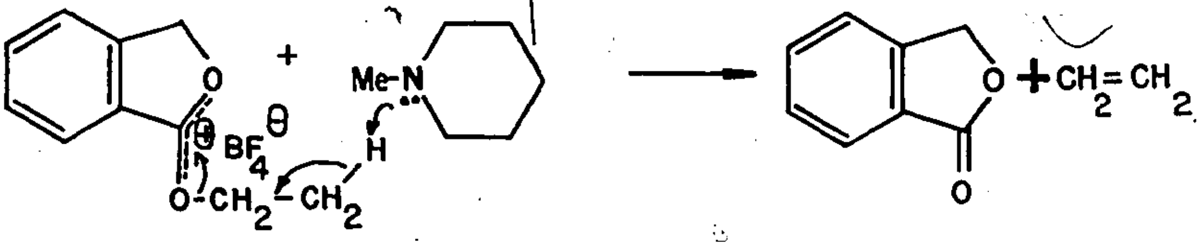


158



159

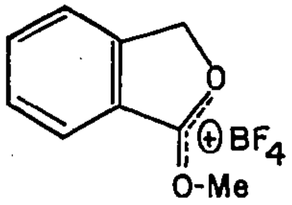
An attempt was next made to generate the intermediate 136 at low temperature from the reaction of 132a with a tertiary amine. However, when the phthalide salt 132a was treated with N-methylpiperidine 160 in methylene chloride at -40°C the product obtained was phthalide 131a which was considered to form by elimination of ethene (Scheme 31).



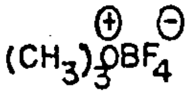
132a. 160 131a

Scheme 31

Attempts to prepare the phthalide salt 161 also failed because of solubility problems associated with trimethyloxonium fluoroborate 162.



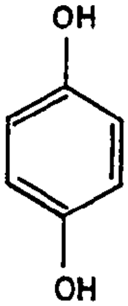
161



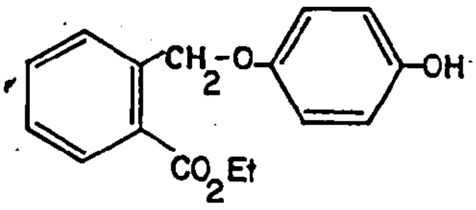
$(CH_3)_3\overset{\oplus}{O}\overset{\ominus}{BF_4}$

162

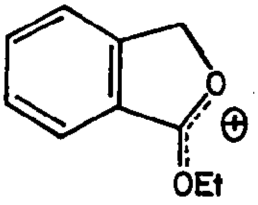
In yet another approach to test the mechanism outlined in Scheme 28, an attempt was made to trap the carbonium ion intermediate 135. For this purpose, 127a was heated in the presence of 1,4-hydroquinone 163. The only product identified from this reaction other than starting material was 164 apparently formed by nucleophilic attack of oxygen at C-3 of the carbonium ion 135. There was no compound isolated resulting from electrophilic attack at carbon on 163.



163



164



135

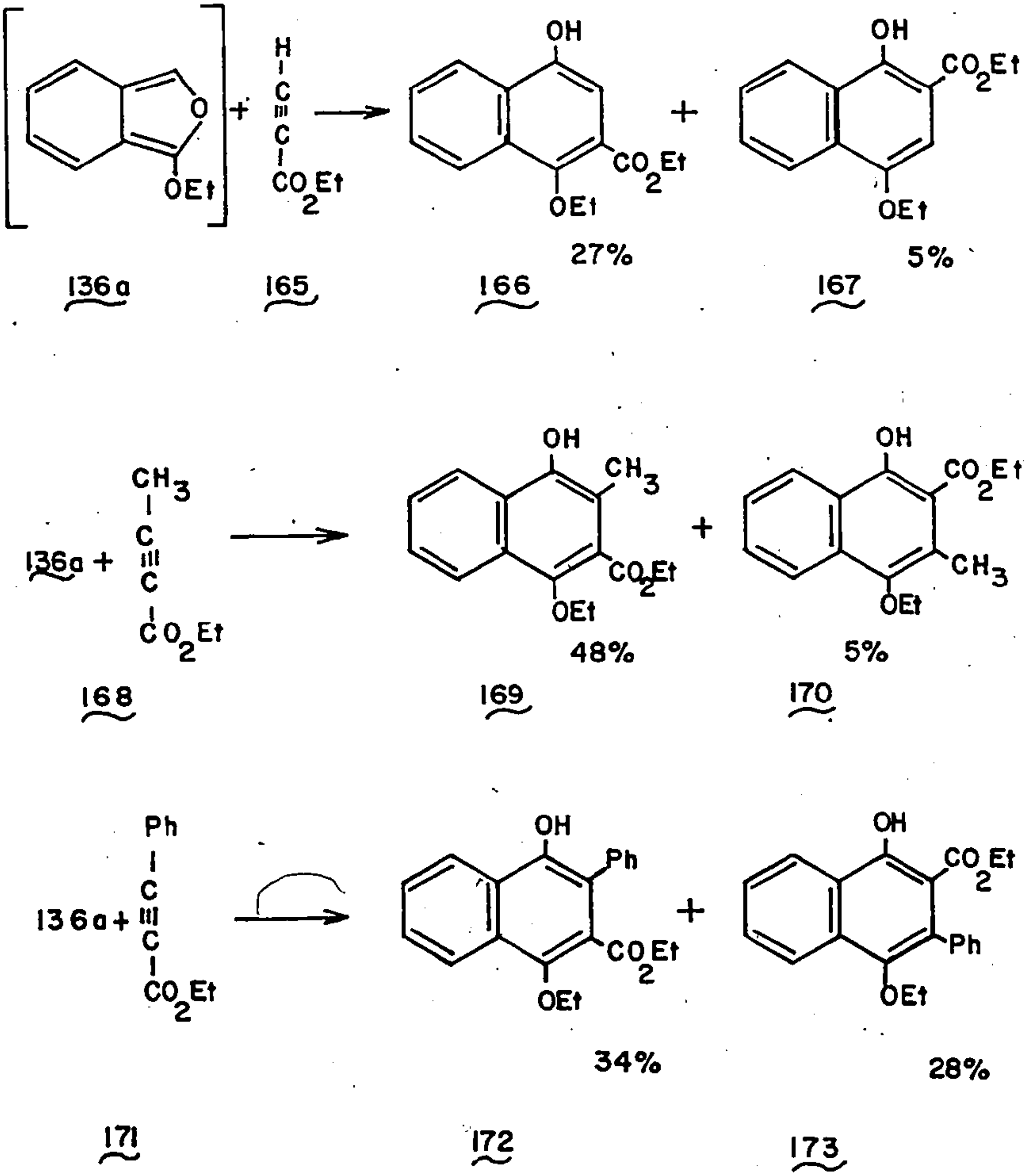
The infrared spectrum of 164 showed a band for a free OH (3600 cm^{-1}) and for an intermolecular hydrogen bonded OH (3420 cm^{-1}) and a band at 1710 cm^{-1} corresponding to an ester carbonyl group. The ^{1}H NMR spectrum of 164 (Figure 7) showed signals corresponding to one ethyl group with peaks at 1.35 and 4.35 δ, characteristic of ethyl in a carboethoxy group. The phenolic proton appears at 5.16 δ and the signal disappears in the presence of D_2O. The benzylic protons are located at 5.38 δ. A multiplet is observed centered at 6.78 δ corresponding to the aromatic protons of the hydroquinone group. The other aromatic protons form a multiplet over the range of 7.1 - 8.2 δ.

The low field region of the ^{13}C NMR spectrum showed a signal attributed to an ester carbonyl group at 167.5 ppm. The aromatic ring carrying the carboethoxy group showed signals for protonated carbon atoms at 127.7, 127.3, 130.8 and 132.8 ppm and for quarternary carbon atoms at 128.2 and 139.7 ppm. The presence of a hydroquinone moiety is indicated by the signals at 116.0 (d) and 116.2 (d) that correspond to the protonated aromatic carbon atoms and 150.2 (s) and 152.8 (s) ppm corresponding to the oxygen substituted carbon atoms. These assignments correlate well with the spectrum of hydroquinone itself 163. The aliphatic region showed signals at 61.2 (t) and 14.2 (q) ppm that can be attributed to the ethoxy group. The benzyl carbon atom produces a signal at 68.9 (t) ppm. The spectroscopic data are in agreement with the assigned structure.

2.4 Reaction of 127a with Unsymmetrical Acetylenes

The question of regioselectivity in Diels-Alder reactions arises when both the diene and dienophile are unsymmetrically substituted. Thus, regioselectivity in the cycloaddition of 127a with unsymmetrical acetylenes such as ethyl propiolate 165, ethyl tetrolate 168 and phenyl propiolate 171 was studied. It was found that "ortho adducts" (vide infra) in these reactions were formed as major products (Scheme 32).

The structures of 166, 167, 169, 170, 172 and 173 are based on their elemental analyses and their spectroscopic properties. It was possible to distinguish between the pairs 166 and 167, 169 and 170, and 172 and 173, by the infrared absorption of the ester group, the chemical shift of the hydroxyl proton in the ^1H NMR spectrum and the chemical shift of the carbonyl group in the ^{13}C NMR spectrum. For example, the infrared spectrum of 166 (Figure 9) showed a band for a normal ester carbonyl group. The ^1H NMR spectrum (Figure 11) showed a peak of 5.90 for a free hydroxyl proton and the ^{13}C NMR spectrum showed a signal at 167.3 ppm which is characteristic of a carbonyl carbon in an ester. In contrast, the infrared spectrum of 167 (Figure 10) showed a band for an ester carbonyl group at 1655 cm^{-1} consistent with an intramolecularly hydrogen-bonded ester function (47). The ^1H NMR spectrum of 167 (Figure 12) showed a peak at 11.70 δ for a hydrogen-bonded hydroxyl proton (48) and the ^{13}C NMR spectrum of 167 showed a peak at 171.1 ppm attributed to a hydrogen-bonded ester function. Similar differences were


OEt
H
C
C
CO2Et
OH
CO2Et
OEt
27%
OH
CO2Et
OEt
5%
136a
165
166
167
CH3
136a +
C
C
CO2Et
OH
CH3
CO2Et
OEt
48%
OH
CO2Et
CH3
OEt
5%
168
169
170
Ph
136a +
C
C
CO2Et
OH
Ph
CO2Et
OEt
34%
OH
CO2Et
Ph
OEt
28%
171
172
173

Scheme 32

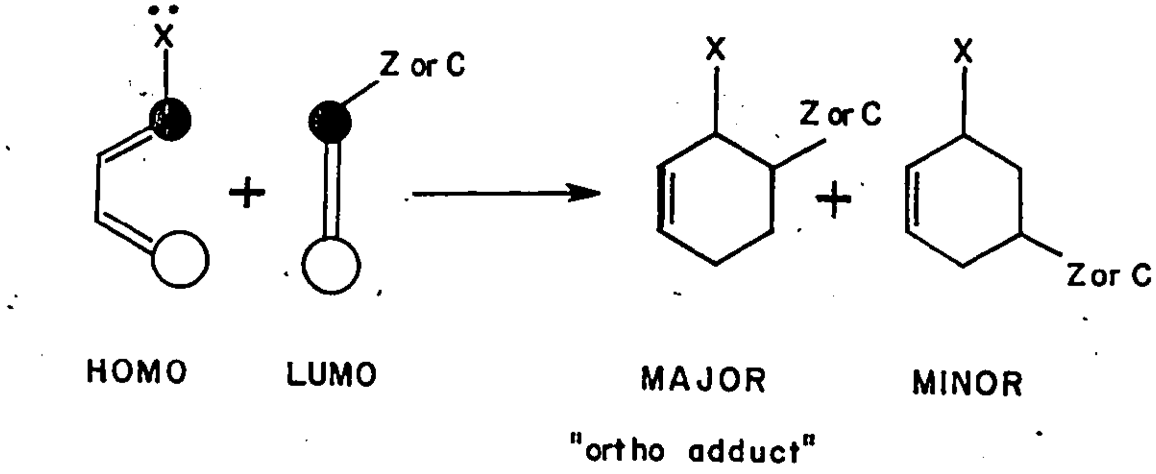
found between 169 and 170 and 172 and 173, as shown in Table 5.

The ^{13}C NMR chemical shifts of 166, 167, 169, 170, 172 and 173 are recorded (Appendix, Table 6). The chemical shifts are in agreement with the proposed structures. The signals of the aromatic carbon atoms have been tentatively assigned by comparison with other substituted naphthalenes.

The preference for "ortho adducts" may be rationalized by using the frontier molecular orbital (FMO) theory (54). In its simplest form the FMO theory predicts that in Diels-Alder reactions between 1-substituted-1,3-butadienes in which X = an electron donating substituent such as NR_2, OMe, Me, etc., and monosubstituted dienophiles in which Z = an electron withdrawing substituent, such as COOR, CN, NO_2, etc., or a conjugated substituent such as phenyl, vinyl, etc., the unoccupied molecular orbital of lowest energy (LUMO) of the dienophile will interact strongly with the highest occupied molecular orbital (HOMO) of the diene. The coefficients of these orbitals are largest at C-4 of the diene and at C-2 of the dienophile. Thus, bonding to give "ortho adducts" is favoured as shown in Scheme 33, where the size of the circle is roughly in proportion to the size of the coefficient. The circles represent the lobes of the p orbitals above the plane of paper, and the shaded and unshaded circles represent orbitals of opposite sign. This symbolism is taken from Fleming (54).

TABLE 5. IR, ^{1}H NMR and ^{13}C NMR data for substituted naphthalenes derived from unsymmetrically substituted acetylenes.

Compound	IR (cm^{-1})		^{1}H NMR	^{13}C NMR
	OH	C=O	OH	C=O
166	3610, 3420	1720	5.90	167.3
167		1655	11.70	171.1
169	3610, 3380	1730	5.50	168.6
170		1655	12.10	172.6
172	3530	1730	5.40	167.4
173		1650	12.10	171.8



Scheme 33

1-ethoxyisobenzofuran 136a may be considered to be analogous to a 1-substituted-1,3-butadiene where the substituent is electron-releasing. Thus, the reaction of 136a with monosubstituted dienophiles containing an electron withdrawing group such as 165 and 168 to give the preferred "ortho adduct" is found to be in agreement with the FMO theory. However, when phenyl propiolate 171 was used as dienophile, the ratio of 172 to 173 is almost 1:1, suggesting that the electron withdrawing effect of the carboethoxy group is counterbalanced by the phenyl group.

2.5 Reaction of 127a With Diethyl Maleate and Maleic Anhydride

In order to extend the study of the reaction of phthalide ortho ester 127a with dienophiles, a series of experiments with activated ethylenes was carried out.

The ortho ester 127a was treated with diethyl maleate 174 in chloroform at 170°C for 72 h in a sealed glass tube. Two products, 178 and 180 (Scheme 34), were formed in approximately 30% and 10% yield, respectively (55). However, when the reaction was carried out at atmospheric pressure for 6 h at 165°C, the product consisted of three compounds which were separated by column chromatography. The first was the trisubstituted naphthalene 178 (48%). The second (larger Rf) was one of the racemates of diethyl 1-hydroxy-4-ethoxy-1,2-dihydronaphthalene-2,3-dicarboxylate 177a (18%). The third compound (smaller Rf) 177b (34%) was an isomer of the previous substance.

The structures of 178 and 180 are assigned on the basis of their spectra. The infrared spectrum of 180 showed two carbonyl bands in the carbonyl region at 1730 and 1655 cm^{-1} attributed to ester absorption. The lower field absorption was assigned as in previous cases to an intramolecularly hydrogen-bonded ester carbonyl group. The ^1H NMR spectrum of 180 (Figure 13) showed a peak at 12.10 δ for a hydrogen bonded hydroxyl proton. The two methyls of the two carboethoxy groups have the same chemical shift and appear as a triplet at 1.40 δ. The methylene protons appear as two overlapped quartets centered at 4.40 and 4.50 δ. The aromatic region showed two multiplets, one of area 3H centered at 7.68 δ, and the other multiplet of area 1H centered at 8.43 δ. There was also a singlet for 1H at 7.45 δ, assigned to H-4. Compound 180 has been converted by ethylation into 178. A multi-step synthesis (56) of 180 has been previously reported but it was not obtained in crystalline form. In another study, the dimethyl ester of 1-hydroxy-2,3-naphthalene-dicarboxylic acid was prepared (57); the spectroscopic properties reported for it are very similar to those of 180.

The ^{13}C NMR spectrum of 180 showed two signals for the carbonyl carbon atoms of the ester groups. The signal at 170.2 ppm is attributed to the internally hydrogen-bonded ester function and the signal at 169.2 ppm to the non-bonded ester group. The other chemical shifts for 180 are recorded in the Appendix, Table 7.

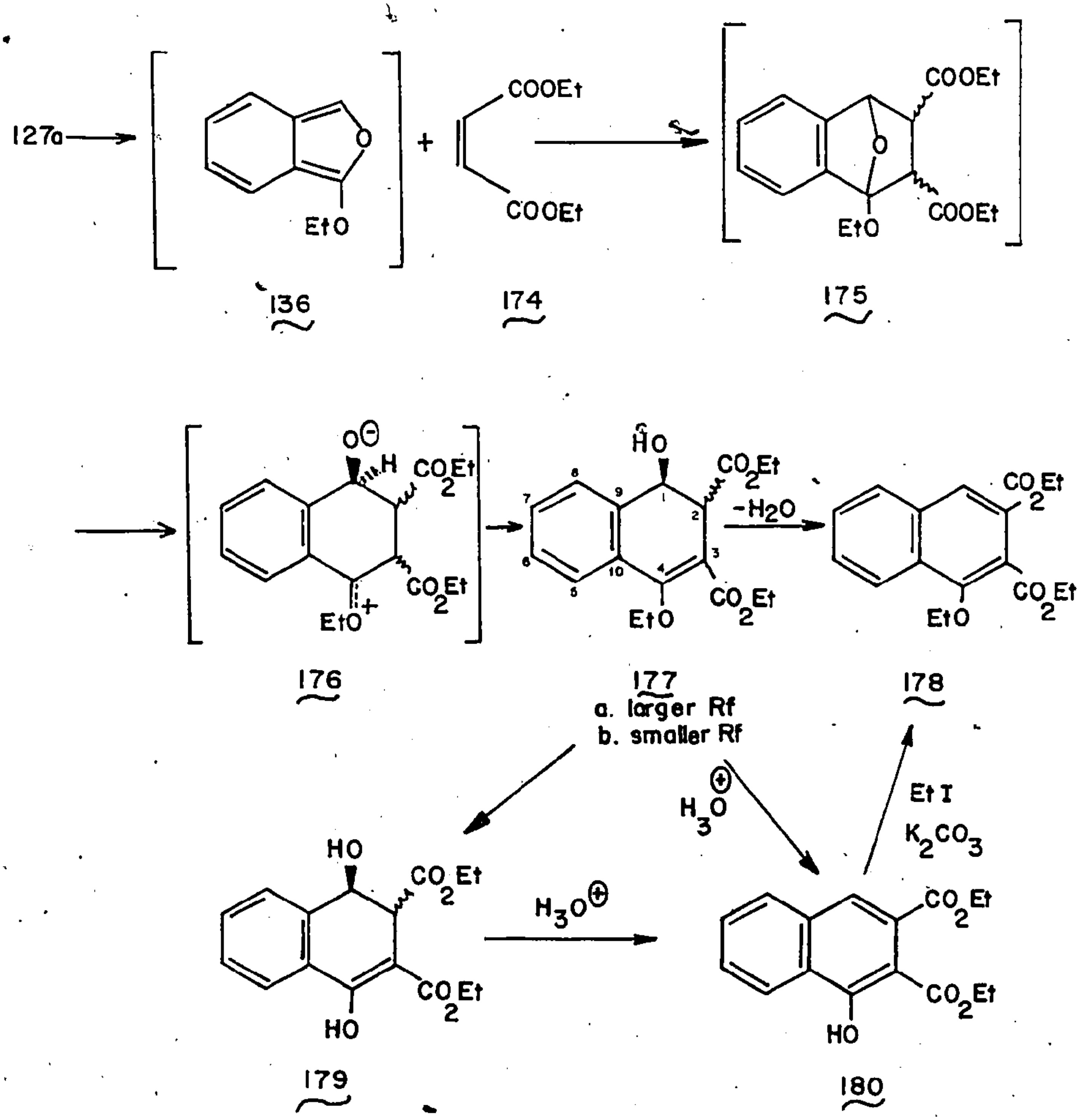
The infrared spectrum of 178 showed only one absorption for the ester carbonyl group at 1730 cm^{-1}. The ^{1}H NMR spectrum of 178 (Figure 14) showed signals attributed to the three ethyl groups at 1.37 (t), 1.38 (t) and 1.43 (t) associated with the methyl and at 4.20 (q), 4.38 (q) and 4.47 (q) associated with the methylene groups. The aromatic region consists of 3 multiplets centered at 7.58, 7.92, and 8.12 δ for 2H, 1H and 1H, respectively. The singlet of the H-4 proton is deshielded (8.32 δ) relative to H-4 in 180.

The ^{13}C NMR chemical shifts of 178 showed two signals for the ester carbonyl group at 165.6 and 167.9 ppm, respectively. The other signals are tabulated in the Appendix, Table 7.

The enol ethers 177a and b were identified on the basis of their spectra. The infrared spectrum of each enol ether, 177a and b showed a band for hydroxyl absorption at 3480 cm^{-1} and a band at 1730 cm^{-1} attributed to ester absorption. The ^{1}H NMR spectrum of 177a (Figure 15) contains three sets of overlapping ethyl resonances with peaks centered at 1.05, 1.38 and 1.42 δ assigned to the methyl groups; the methylene groups appear as two overlapping quartets centered at 4.04 and 4.37 δ. Also overlapped with the methylene peaks is the signal for the proton at C-2 giving a total of 7H in this region. The benzylic proton appears as a broad doublet of doublets with a coupling constant, $J = 6.0$ Hz, due to vicinal coupling to H-2 and to the hydroxyl proton. The latter signal was not located in the spectrum. The broad signal ascribed to H-1 collapsed to a doublet, $J = 6.0$ Hz, on addition of D_2O. The four aromatic protons form a multiplet over the range 7.20 - 7.80 δ. When the ^{1}H NMR spectrum of 177a was run in dimethylsulfoxide (DMSO-d_6), the benzylic proton was shifted to 5.16 δ and appeared as a triplet with $J = 6.0$ Hz. This signal collapsed to a doublet with $J = 6.0$ Hz when D_2O was added suggesting a coupling to the hydroxyl proton with the same coupling constant as with H-2. The hydroxyl proton appeared as a doublet with $J = 6.0$ Hz at 5.80 δ in DMSO-d_6. This signal disappeared when D_2O was added. The ^{1}H NMR spectrum of 177b (Figure 16) had a spectrum similar to 177a except that vicinal coupling between the benzylic proton on C-1 and H-2 is now 4.5 Hz. This is indicative of the change in configuration at C-2 resulting in a different dihedral angle between H-1 and H-2.

The ^{13}C NMR spectra of 177a and 177b (Appendix, Table 7) were also found to be similar. The aliphatic region of both spectra showed the presence of two methine carbons in which C-1 of 177b is shielded by -0.5 ppm while C-2 is deshielded by 4.2 ppm relative to the same centers in 177a. Also present in this region are other signals corresponding to the carbon atoms of the ethoxy groups. The low field region showed that the carbonyl carbon at C-2 of 177a is deshielded by 1.7 ppm with respect to 177b. It is possible that this difference may be due to some degree of hydrogen bonding of the carboethoxy and the hydroxyl group. However, it would be unwise from these data (^{1}H NMR and ^{13}C NMR spectra) to attempt to assign the relative configuration at C-2 in 177a and its diasteroisomer 177b.

The formation of 177, 178 and 180 can be rationalized through the intervention of 1-ethoxyisobenzofuran 136 (Scheme 34), which undergoes cycloaddition with 174 to give the intermediate 175. This intermediate can undergo C-O bond cleavage to the zwitterion 176, as in the previous case (see Scheme 28), which then collapses to the enol ethers 177. The isolation of the compounds 177 is indirect evidence for the formation of the tricyclic intermediate. From the ratio of 177a to 177b, one might be tempted to draw conclusions about the exo-endo ratio of the addition. Aside from the fact that isomerization might occur during workup, the following remarks are relevant. It has been found that the exo-endo ratio of adducts from the various cycloaddition reactions of isobenzofurans with dienophiles varies. Whereas Kende (35), Wiersum (33) and Bornstein (58) have observed the predominance of endo isomers in these reactions, Ibata (53)


127a
EtO
COOEt
COOEt
136
174
175
O⊖
H
CO2Et
CO2Et
EtO+
176
HO
1
2
3
4
5
6
7
8
9
10
177
a. larger Rf
b. smaller Rf
-H2O
178
H3O⊕
Et I
K2CO3
HO
179
H3O⊕
180

Scheme 34

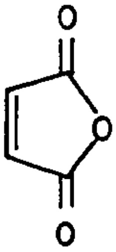
found an endo-exo ratio of 1:1 in adducts, 150. In all cases the endo-exo ratio was determined by NMR spectral analysis. The geometry in the exo adduct prevents the coupling of the protons at the bridge junction and the adjacent proton in the NMR spectrum. Such coupling is observed in the endo adducts (33, 35). Since no general rule can be formulated for such reactions and since the tricyclic compound 175 was not isolated, it is not possible to predict the endo-exo ratio in the reaction of 136 with 174.

In another experiment, the compound 179, together with 178 (15%), was isolated from the reaction of 127a with 174, as a mixture of diasteroisomeric enolic forms in 65% yield. The product 179 apparently arises by hydrolysis of 177 in the course of silica gel column chromatography. The infrared spectrum of 179 showed bands for hydroxyl absorption at 3480 cm^{-1} and carbonyl absorptions at 1665 and 1735 cm^{-1}. Although the ^1H NMR spectrum of 179 was complex, it showed peaks at 2.80 and 12.80 δ for free and hydrogen-bonded hydroxyl protons, respectively. These signals collapsed when D_2O was added. Treatment of 179 with p-toluenesulfonic acid yielded 180 by dehydration in quantitative yield.

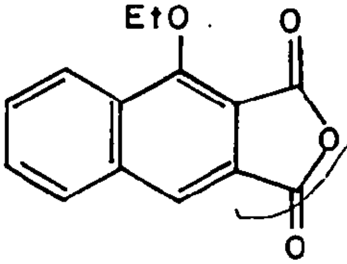
It was also found that the enol ethers 177a and 177b on treatment with acid yielded 180 which indicated that they undergo hydrolysis of the enol ether faster than they undergo dehydration. None of the compound 178 was observed on dehydration of 177a or 177b with p-toluenesulfonic acid in benzene.

When maleic anhydride 70 was used as dienophile, one product

181 was separated by crystallization in 56% yield.



70



181

The infrared spectrum of 181 showed two bands in the carbonyl region at 1845 and 1785 cm^{-1} attributed to the anhydride group (47). The ^{1}H NMR spectrum of 181 (Figure 17) showed a peak for the ethoxy group at 1.55 and 4.82 δ corresponding to methyl and methylene groups, respectively. In the aromatic region, there was a multiplet between 7.50 - 8.20 δ for 3H, a multiplet centered at 8.47 δ for 1H and a singlet at 8.07 δ for 1H assigned to H-4.

The ^{13}C NMR spectrum showed a signal at 72.9 (t) and 16.0 (q) ppm that can be attributed to the ethoxy group. The low field region showed two signals for the anhydride carbonyl group at 161.5 and 163.5 ppm, respectively. The higher field signal is assigned to C-2 carbonyl carbon atom, because of the steric effect of the ethoxy group. The complete spectrum is tabulated in the Appendix, Table 7.

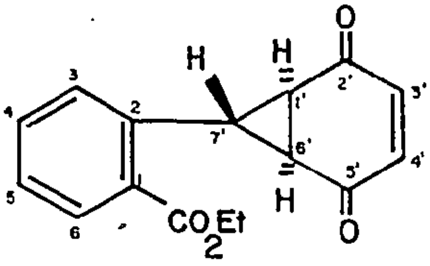
The reactions described above showed that phthalide ortho esters may be used as intermediates to prepare 1,2,3-trisubstituted-naphthalenes or 1,2,3,4-tetrasubstituted 1,2-dihydronaphthalenes. In the next section, an unusual reaction between quinones and phthalide ortho ester is discussed.

2.6 Reaction of 127a and 127b with 1,4-benzoquinone and 1,4-naphthoquinone

In contrast with the reaction of acetylenes and alkenes with 127 to give tetrasubstituted naphthalenes and trisubstituted naphthalenes, respectively, quinones were found to react with 127 in an unusual manner. The major products were p-homoquinones, instead of the tricyclic or tetracyclic compounds expected from a normal cycloaddition reaction. The term, p-homoquinone, has been used by Dreiding et al. (59, 60) and Adam et al. (61) to describe systems in which a methylene or substituted methylene unit has been added across the double bond of a quinone. For this reason and for the sake of brevity compounds 183, 184 and 185 will be referred as p-homobenzoquinones and 186, 188 and 189 as p-homonaphthoquinones (vide infra). The systematic names according to IUPAC rules will be given in the experimental section.

Treatment of 127a with 1,4-benzoquinone 182 at atmospheric pressure for 45 minutes gave the unexpected p-homobenzoquinone 183 in 29% yield. It was not possible to identify the other components of the reaction mixture. Similar treatment of 127b with 182 afforded the diastereoisomeric mixture of p-homobenzoquinones 184 and 185, isolated in 42% and 0.5% yield, respectively.

When 127a was treated with 1,4-naphthoquinone 66 at atmospheric pressure at 140°C for 20 minutes a mixture of two compounds was obtained.



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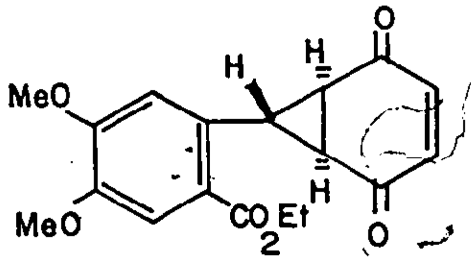

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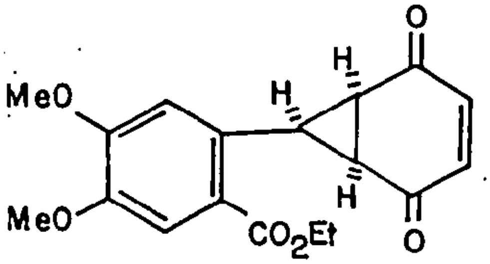

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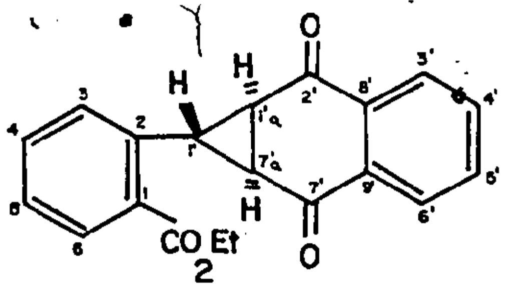

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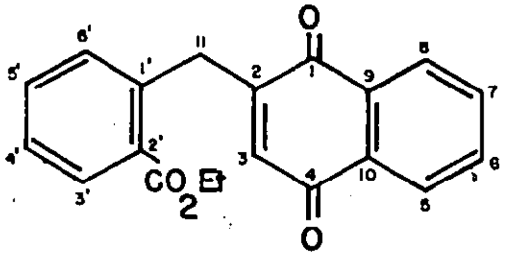

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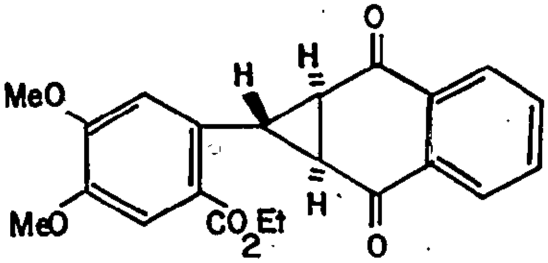

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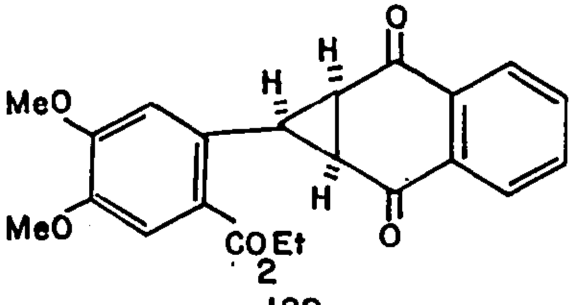
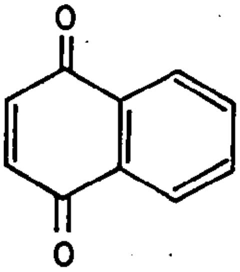
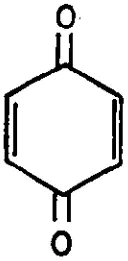


189

In addition to the p-homonaphthoquinone 186 (32%) a new compound identified as 2-(2'-carboethoxybenzyl)-1,4-naphthoquinone 187 was isolated in 28% yield. In the case of the reaction of 127b with 66 a mixture of trans and cis p-homonaphthoquinones was obtained in 48% and 17% yield, respectively. The diastereoisomeric mixture of 188 and 189 was separated by reversed phase chromatography on a Lobar column.



66



182

The structures of compounds 183, 184, 185, 186, 187, 188 and 189 were assigned on the basis of their elemental analyses and spectroscopic properties. The infrared spectra of these compounds showed two characteristic bands in the carbonyl region, the first in the range 1710 - 1725 cm^{-1} attributed to the ester carbonyl group and the other in the range 1675 - 1685 cm^{-1} assigned to the 1,4-dienone group (47). The ^{1}H NMR spectra of the p-homoquinones 183, 184, 185, 186, 188 and 189 showed that chemical shifts for the cyclopropane protons fell into the same range (Table 8). In the ^{13}C NMR spectra of these compounds, the chemical shifts of the cyclopropyl carbon atoms and of the carbon atoms of the carbonyl groups are also similar (Table 9).

In the following, a detailed analysis is given of the NMR spectrum of 183. This study established the presence of the cyclopropane ring and the substitution pattern in this compound. The spectra of the other compounds are not considered in the same detail and only similarities and differences to 183 are referred to. The ^{1}HNMR spectrum of 183 (Figure 18) showed two signals corresponding to one ethyl group with peaks at 1.37 and 4.38 δ, characteristic of ethoxy in an ester group. The absorption of the methine protons, H-1' and H-7', was assigned to a doublet at 2.83 δ with $J = 5.4$ Hz. These two protons are equivalent because of a plane of symmetry that bisects the cyclopropane ring. The methine proton at C-7' appears as a triplet at 4.02 δ with $J = 5.4$ Hz. The configuration of the cyclopropane moiety was determined on the basis of the value of the coupling constant between the equivalent protons H-1' and H-6' on one hand and H-7' on the other. From the geminal H-C-H bond angles of 114.5 - 118^0 for cyclopropanes (62) the corresponding dihedral angles are calculated to be 144^{0}C for trans-cyclopropyl hydrogens and 0^0 for cis-cyclopropyl hydrogens. Theoretical treatment of spin-spin coupling (63) predicts, for these dihedral angles, that vicinal coupling constants will be higher for cis-hydrogens than for trans-hydrogens in cyclopropanes. These predictions have been found to be in agreement with the observed values. For example, Dreiding et al. (60) have reported values J_{cis} in the range 9.3 - 10 Hz and J_{trans} in the range 5.0 - 5.4 Hz in cyclopropane

TABLE 8. ${}^1H$ NMR chemical shifts and coupling constants of p-homoquinones.

Compound	H-1',6'	H-7'	H-1'a,7'a	H-1'	Coupling Constant (Hz)	
183	2.83	4.02			${}^3J_{1',7'}$	5.4
184	2.77	3.97			${}^3J_{1',7'}$	5.3
185	2.87	3.55			${}^3J_{1',7'}$	9.0
186			3.01	3.85	${}^3J_{1'a,7'a}$	5.3
188			2.96	3.83	${}^3J_{1'a,7'a}$	5.3
189			3.10	3.70	${}^3J_{1'a,7'a}$	9.8

TABLE 9. ^{13}C NMR chemical shifts of p-homoquinones

Carbon	183	184	186	188	189
COOEt	166.4	166.2	166.8	166.8	
C-2',5'	193.5	193.5			
C-2',7'			192.2	193.3	193.0
C-1',6'	35.8	36.0			
C-7'	36.3	36.8			
C-1'a,7'a			36.4	36.7	34.0
C-1'			36.0	36.4	34.4

rings in p-homoquinone systems. The three bond coupling constant of 5.4 Hz between the equivalent protons H-1' and H-6' and H-7' is in the range observed for trans protons in a cyclopropane and suggests a trans configuration of the cyclopropane ring. The olefinic protons of the quinone group appear as a singlet at 6.60 δ. The aromatic protons showed two multiplets, the first centered at 7.40 δ for 3H and assigned to H-3, H-4 and H-5, and the other centered at 8.05 δ for 1H corresponding to the proton at C-6.

The aliphatic region of the ^{13}C NMR spectrum of 183 showed four signals. The signals at 61.5 (t) and 14.3 (q) ppm were assigned to the methyl and methylene carbon atoms of the ethyl ester. The other two signals were assigned to the cyclopropane carbon atoms, the higher intensity signal at 35.8 ppm to C-1' and C-6' and the signal at 36.6 ppm to C-7'. The olefinic carbon atoms (C-3' and C-4') were assigned to the signal at 138.0 (d) ppm. The low field region showed two signals. The signal at 193.5 ppm is attributed to the carbonyl carbon atoms of the quinone group and the signal at 166.4 ppm is assigned to the carbonyl carbon atom of the ester group. The other signals were assigned tentatively and they are tabulated in the Appendix, Table 10.

The NMR and other spectroscopic data indicate strongly that this homoquinone has structure 183. This structure was confirmed by an X-ray crystallography study, carried out by Dr. C. J. L. Lock and R. Faggiani (64). Their work established beyond question the overall structure and particularly the trans-configuration of the p-homobenzoquinone 183. With the structure of 183 secure it was a simple matter to assign the structures of the other p-homoquinones.

Examination of the ^{1}H NMR spectrum of 184 (Figure 19) showed that the aliphatic region was similar to that of 183 except for the presence of a singlet of 6H at 3.92 δ assigned to the two methoxy groups. The chemical shifts and the coupling constant of the cyclopropyl protons are recorded in Table 8. The aromatic protons appear as two singlets at 7.35 and 6.60 δ, respectively.

In the case of 185 the ^{1}H NMR spectrum (Figure 20) had a pattern similar to its isomer 184 differing only in the coupling constant between the equivalent protons H-1' and H-6' and H-7'. In 185 the coupling is 9.0 Hz compatible with a cis configuration of the cyclopropane ring.

The ^{13}C NMR spectrum of 184 (Appendix, Table 10) in the aliphatic region showed an additional signal, relative to 183, at 56.2 ppm corresponding to the two methoxy carbon atoms. The other aliphatic carbon atoms are essentially unchanged from those of 183 (Table 9). Insufficient material was available to obtain a ^{13}C NMR spectrum of 185.

The resonances of the aliphatic protons in the ^{1}H NMR spectrum of 186 (Figure 21) follow from direct comparison to 183. The aliphatic region is similar to that of 183 differing only in the chemical shifts of the cyclopropane protons (Table 8). The aromatic protons appear as a multiplet over the range 7.20 - 8.22 δ.

In the ^{13}C NMR spectrum of 186, the resonances of the bridgehead carbons 1'a and 7'a appear at lower field than the benzylic carbon at C-1' (Table 9). The absorptions of the carbon atoms of the 1,4-naphthoquinone moiety were assigned by comparison to the ^{13}C NMR spectrum of 1,4-naphthoquinone 66 (65) and they are tabulated in the Appendix, Table 10.

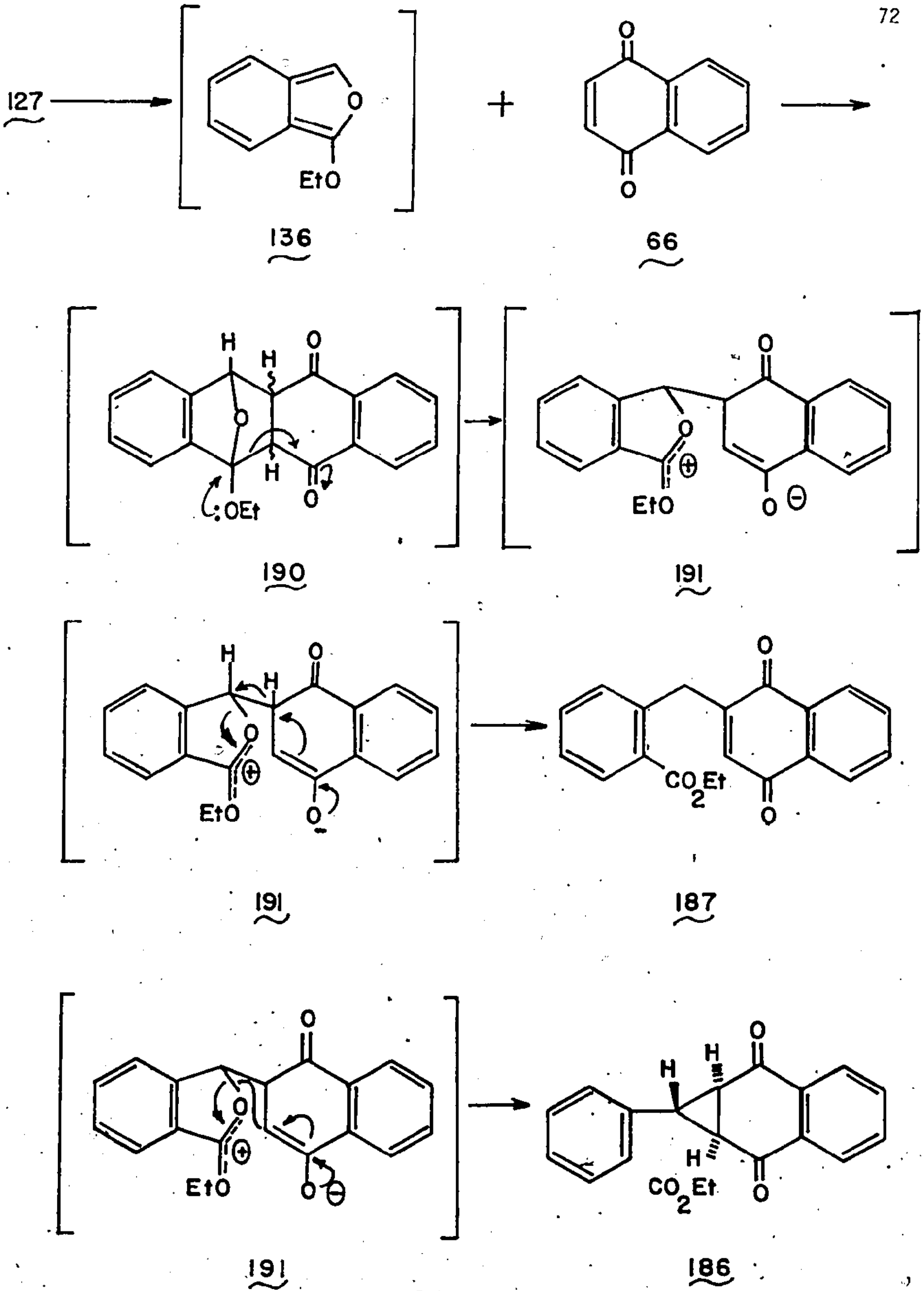
The diastereoisomeric compounds 188 and 189 have similar ^{1}H NMR spectra (compare Figures 23 and 24). They differ significantly only in the value of the coupling constant of the cyclopropane protons (Table 8) reflecting their trans and cis configuration.

Examination of the ^{13}C NMR spectra of 188 and 189 showed that the chemical shifts of the bridgehead carbon atoms (C-1'a and C-7'a) and C-1' for 189 are in inverse order to those for 188 (see Table 9). Otherwise, the spectra are very similar (see Appendix, Table 10).

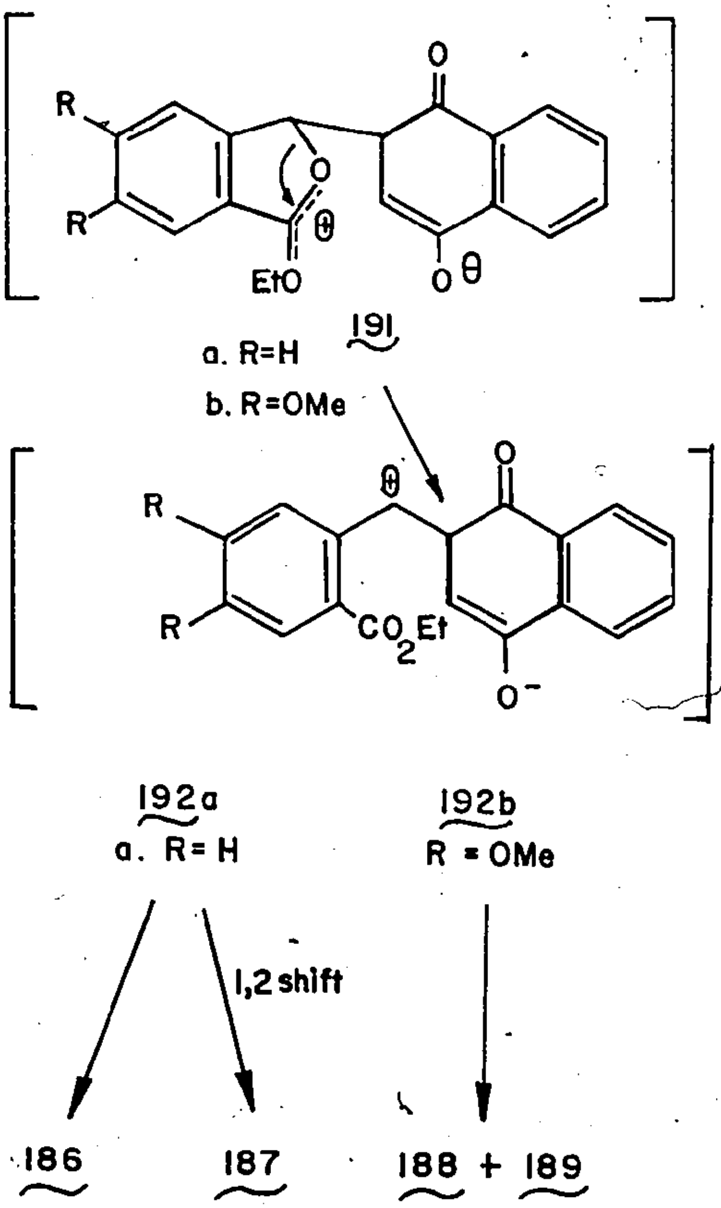
The ^{1}H NMR spectrum of 187 (Figure 22) has a number of signals which are similar to those of 186. The methyl and methylene protons of the carboethoxy group appear at 1.28 and 4.26 δ, respectively. The aromatic region has three multiplets, the first is centered at 7.41 δ for 3H, the second at 7.73 for 2H and the third centered at 8.10 δ for 3H. The major difference between 187 compared to 186, 188 and 189 is the absence of signals associated with the cyclopropane ring and the appearance of two new signals. The first is at 4.30 δ of area 2H and the other at 6.28 δ of area 1H, both of which showed a small coupling. Irradiation of the 4.30 peak produced a sharpening of the signal at 6.28. This suggests the presence of allylic coupling between an olefinic proton at 6.28 δ and benzylic methylene protons at 4.30 δ. The presence of a methylene carbon atom was confirmed by the ^{13}C NMR spectrum of 187 which showed a signal at 34.3 ppm. This signal appeared as a triplet in the off-resonance spectrum. The aliphatic region also showed signals for the methyl and methylene carbon atoms of the ethoxy group at 14.2 and 61.0 ppm, respectively, but no other signals were present. The low field region had three signals; the first at 166.8 ppm corresponding to the carbonyl carbon atom of the ester group, and the other two at 185.0 and 185.2 ppm attributed to the non-equivalent naphthoquinone carbonyl carbon atoms. The remaining signals are recorded in the Appendix, Table 10.

The formation of the products discussed above can be rationalized on the basis of the reactions outlined in Scheme 35. The intermediate 190 is similar to the intermediates proposed for the Diels-Alder addition of acetylenes or alkenes to 136. The intermediate 190 is considered to undergo simultaneous C-C bond cleavage and enolization to form the zwitterion 191. This may collapse to 187 by a 1,2 hydride shift with simultaneous C-O bond cleavage. Alternatively, this zwitterion may undergo intramolecular nucleophilic substitution by attack of the enol at the benzylic carbon to give the cis-ring fused p-homoquinone 186. The major isomer in these reactions has the benzylic hydrogen trans to the bridgehead hydrogens. This would be the result expected if the adduct 190 had the endo configuration. A cis arrangement of the hydrogens would be the result from an exo adduct undergoing a similar series of reactions.

Another possible route to products beginning from 191 is outlined in Scheme 36. In this case, it is proposed that 191 is transformed to zwitterion 192a or 192b. The intermediate 192a may then


127
EtO
136
66
H
H
H
O
O
:OEt
190
O
O
EtO
O
191
H
H
O
O
EtO
O
191
O
CO_2Et
O
187
O
O
EtO
O
191
H
H
O
H
CO_2Et
O
186

Scheme 35


191
a. R=H
b. R=OMe
CO2Et
192a
a. R= H
192b
R = OMe
1,2 shift
186
187
188 + 189

Scheme 36

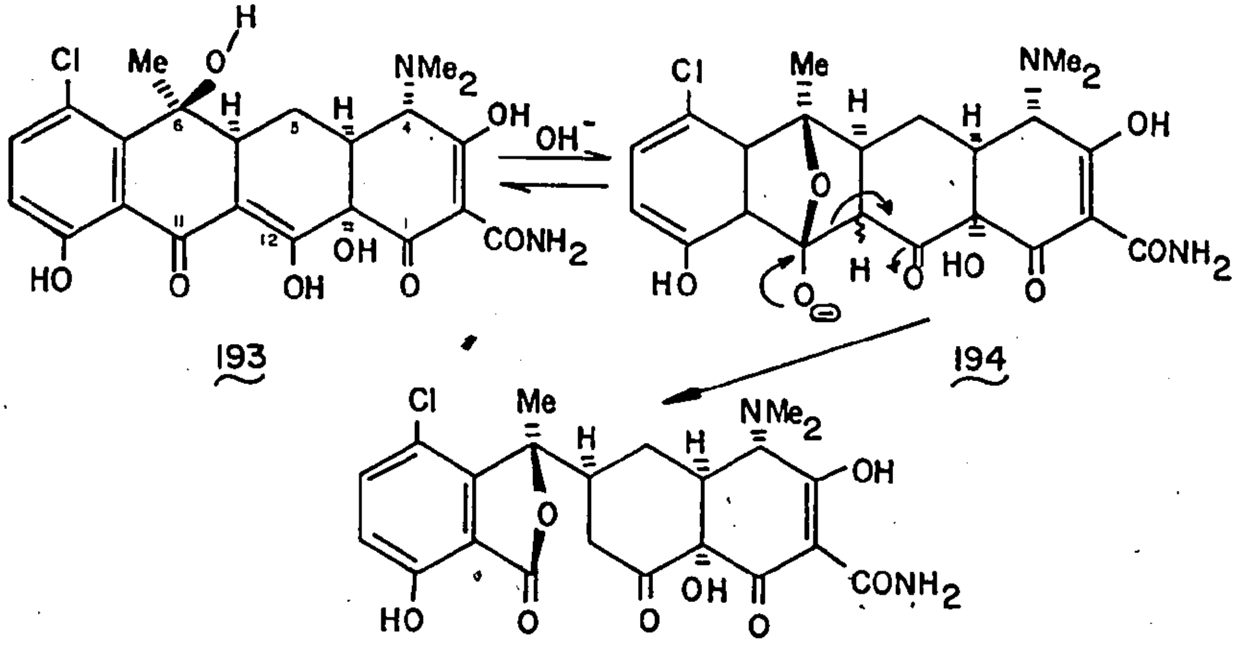
collapse by 1,2 hydride shift to 187 or by attack at the benzylic carbon to 186. In the case of 192b, collapse to a mixture of 188 and 189 would occur. The trans isomer is sterically less crowded than the cis isomer and would be expected to predominate. Thus, there would be no dependence of the isomer ratio on the original endo-exo ratio in the addition of 136 to 66.

Similar types of C-C bond cleavage, followed by enolization, have been reported before. For example, it is known that compounds in the tetracycline family such as chlorotetracycline 193 (Scheme 37) undergo rearrangement to phthalide derivatives called isotetracyclines, e.g. isoaureomycin 195, when they are treated with aqueous base under mild conditions (66). The rearrangement is initiated by nucleophilic attack of the C-6 OH group on the C-11 ketone to give the hemiketal intermediate 194. This intermediate now undergoes C-C bond cleavage and enolization to the isoaureomycin 195.

Also, Eugster and Bosshard (67) have reported that the addition of furan 196 to acetyl-1,4-benzoquinone yields an unexpected product 201. The formation of 201 can be explained by a rearrangement of the normal adduct in its enol form 199, as shown in Scheme 38.

From the two examples given above, it is apparent that the intermediates proposed for the two reactions are related to the intermediate 190. All the intermediates are unstable and undergo C-C bond cleavage accompanied by enolization.

The possibility that the formation of the compounds 183, 184, 185, 186, 187, 188 and 189 might involve the carbene intermediate 202

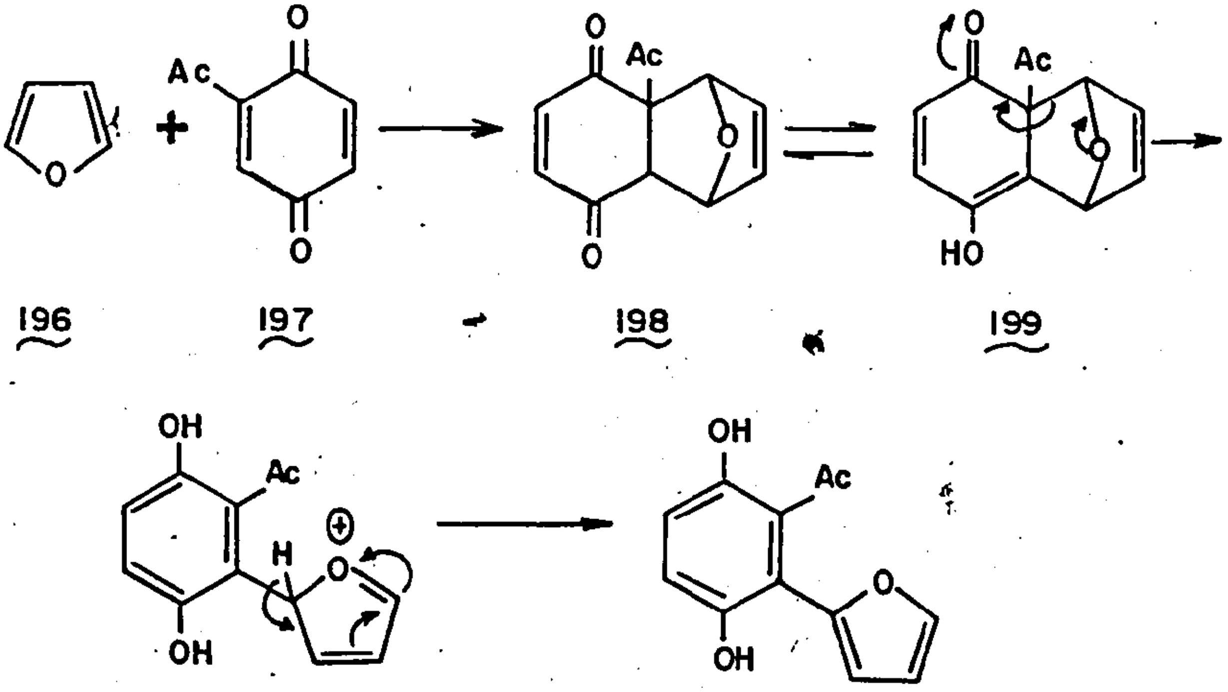


193

194

195

Scheme 37



196

197

198

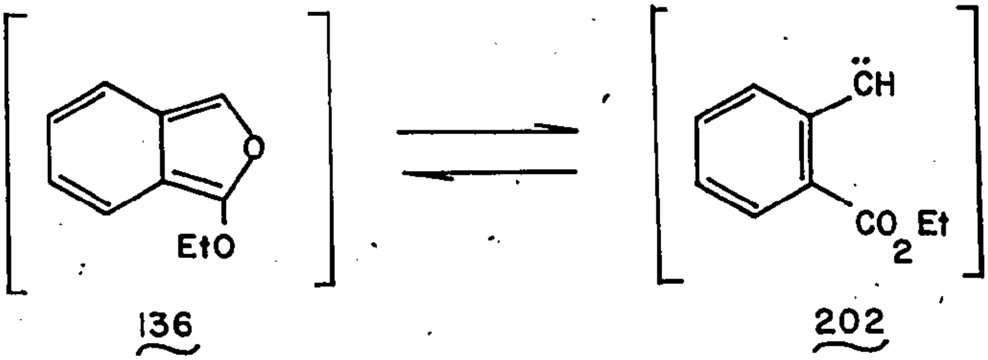
199

200

201

Scheme 38

(Scheme 39) was also considered. Hamaguchi and Ibata had already proposed an interrelationship between a carbene and an isobenzofuran. In this case, intermediate 202, in equilibrium with 136, might undergo C=C bond insertion to yield the p-homoquinones or C-H bond insertion to give the compound 187. In order to test for the formation of 202 trapping experiments with cyclooctene and 1-phenyl-1-propyne were carried out. However, no reaction was found to occur when 127a and cyclooctene or 127a and 1-phenyl-1-propyne were heated together under a variety of conditions.



Scheme 39

It was disappointing not to obtain the tri and tetracyclic adducts from the reactions of phthalide ortho esters with quinones. Such adducts would have possessed the basic skeleton of compounds that have chemotherapeutic properties such as anthracycline compounds. However, this method provides a new route for the preparation of p-homoquinones.

CHAPTER 3

EXPERIMENTAL

Apparatus, Methods and Materials

Melting points were recorded on a Kofler micro hot stage apparatus and are uncorrected. Infrared spectra (IR) were recorded on a Perkin Elmer 283 spectrophotometer in chloroform solution unless otherwise stated. The ^{1}H NMR spectra were recorded on a Varian EM-390 or Bruker WH-90 Fourier transform spectrometer. Unless otherwise specified, the samples were dissolved in chloroform-d_1 using tetramethylsilane (TMS) as the internal standard. The chemical shifts were measured in relation to TMS and are quoted in δ values. The symbols s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet are used in reporting spectra. The ^{13}C NMR spectra were recorded on a Bruker WH-90 Fourier transform spectrometer at 22.62 MHz. Some spectra were also recorded on a Bucker WP-80 Fourier transform spectrometer at 20.115 MHz. Mass spectra were routinely run on all samples to check their molecular weight either on a C.E.C. 21-110B double focussing or a V.G.Micromass 7070 F mass spectrometer. Samples were introduced through a direct inlet system and run at 70 eV. High resolution mass spectrometry was used to confirm the composition of several compounds and mass measurements were made by procedures described elsewhere (68). Analytical thin layer chromatography was performed on Pre-coated TLC silica gel plates (60F 254, Merck). Preparative thin layer chromatography was performed on Pre-coated PLC silica gel plates (60F 254, Merck) with layer thickness 2 mm. For column chromatography silica gel (60F 254, Merck), silica gel (Baker, 60-200 mesh) and alumina neutral (Fisher, activity I, 80-200 mesh) were used. Reverse phase chromatography was performed on TLC plates (KC_{18} Whatman) and on a Lobar prepacked column size A (240-10) LiChroprep RP-8 (40-63 μm) for liquid chromatography (Merck).

The microanalyses were performed by Microanalytical Laboratories, Ltd., Toronto, Ontario and Guelph Chemical Laboratories, Ltd., Guelph, Ontario.

1,2-dichloroethane and methylene chloride were dried and distilled from phosphorus pentoxide. Tetrahydrofuran was dried by refluxing and distilling from sodium and benzophenone under dry nitrogen, and was collected directly from the still just prior to use.

Triethyloxonium fluoroborate 133

Compound 133 was prepared by the method of Meerwein (44). Yield: 92%. mp 91-92°C. Lit. mp 91-92°C.

Trimethyloxonium fluoroborate 162

Compound 162 was prepared by the method of Curphey (69). Yield: 92-95%. mp 178-180°C. Lit. 180°C.

O-Ethylphthalide Fluoroborate 132a

Phthalide 131a (8.8 g, 6.56 m mole) and triethyloxonium fluoroborate 133 (12.5 g, 6.57 m mole) in 15 ml of dry 1,2-dichloroethane were stirred for 48 h at room temperature in a dry box. The solid was separated by filtration (14.3 g, 88%) and washed with 1,2-dichloroethane and dry ether. It melted at 106-108°C (Lit. (43) 107-108°C).

^{1}H NMR(CD_3NO_2): 1.20 (t, 3H, OCH_2CH_3, J = 6.0 Hz), 4.76 (q, 2H, OCH_2CH_3, J = 6.0 Hz), 5.83 (s, 2H, Ar-CH_2) and 7.16-7.86 (m, 4H, aromatic).

1,1-Diethoxyphthalan 127a

O-ethylphthalide fluoroborate 132a (14.3 g, 5.27 m mole) was added at room temperature to a solution of sodium ethoxide in ethanol (prepared from 2.5 g of sodium in 50 ml of absolute ethanol) under a nitrogen atmosphere. The solution was stirred for 1 h, then quenched with 50 ml of 15% aqueous sodium carbonate and extracted thoroughly with ether. The extract was then dried over K_2CO_3, filtered, evaporated, and distilled under vacuum (bp 60°C at 0.1 mm Hg) to give 11.3 g (94%) of 127a.

^{1}H NMR: 1.15 (t, 6H, 2 x OCH_2CH_3, J = 6.0 Hz), 3.25-3.85 (m, 4H, 2 x OCH_2CH_3), 5.03 (s, 2H, ArCH_2), and 7.20-7.50 (m, 4H, aromatic). (Fig. 1).

HRMS: Calc. for $C_{12}H_{16}O_3$: 208.109; Found: 208.110.

5,6-Dimethoxy-1,1-diethoxyphthalan 127b

5,6-dimethoxyphthalide 131b (14.0 g, 72.1 m mole) and triethyloxonium fluoroborate 133 (15.0, 79.0 m mole) were dissolved in 25 ml of dry 1,2-dichloroethane and stirred at room temperature for two days under an argon atmosphere. The dark solution was transferred to a dropping funnel and added to a solution of sodium ethoxide in ethanol (prepared from 3 g of sodium in 70 ml of absolute ethanol) under a nitrogen atmosphere at -20°C. After completion of the addition the reaction mixture was allowed to warm slowly to room temperature and then was quenched with 100 ml of 15% aqueous sodium carbonate. The resulting solution was extracted with methylene chloride. The extract dried over K_2CO_3, and the solvent evaporated to give a yellow oil which was distilled (bp 121°C at 0.05 mm Hg) to yield 14 g (72%) of 127b.

^{1}H NMR: 1.18 (t, 6H, 2 X $OCH_2\underline{CH_3}$, J = 6.0 Hz), 3.30-3.80 (m, 4H, 2 X $O\underline{CH_2}CH_3$), 3.92 (s, 6H, 2 X $O\underline{CH_3}$), 5.02 (s, 2H, $Ar\underline{CH_2}$), 6.77 (s, 1H, aromatic), 6.95 (s, 1H, aromatic). (Fig. 2).

Anal. Calc. for $C_{14}H_{20}O_5$: C, 62.68; H, 7.52%.

Found: C, 62.59; H, 7.64%.

HRMS: Calc. for $C_{14}H_{20}O_5$: 268.131; Found: 268.131.

3-phenylphthalide 155

Compound 155 was prepared by the method of Ullmann (70). Yield 75%. m.p. 115-116°C. Lit 115-116°C (70).

3-Chlorophthalide 156a

Compound 156a was prepared by the method of Gabriel (71). Yield 70%. m.p. 61-63°C. Lit 61°C.

3-Bromophthalide 156b

Compound 156b was prepared by the method of Koten and Sauer (72). Yield 80%. m.p. 79-81°C. Lit 78-80°C.

Attempts to prepare 3-phenyl-1,1-diethoxyphthalan 153

Procedures similar to those used to prepare 127a or 127b were investigated. However, the only products recovered from the reaction mixtures were starting materials.

Attempts to alkylate 3-bromo or 3-chlorophthalide 156

Attempts to alkylate 156a or 156b in the same way that 131a was alkylated afforded black solutions from which identifiable materials were not obtained.

Reaction of 1,1-diethoxyphthalan 127a with dimethyl acetylenedicarboxylate 106

In a Carius tube were placed 500 mg (2.93 m mole) of 127a and 434 mg (3.05 m mole) of 106 in 5 ml of chloroform. The tube was cooled and sealed under vacuum, then heated in a furnace for 6 h at 170°C. The tube was cooled, opened and the contents removed. Upon evaporation of the solvent the oily residue was subjected to high vacuum distillation to remove the more volatile starting material. The product was collected as an oil (560 mg, 76%), crystallized from dry ether and melted at

85-86^{0}C. It proved to be dimethyl 1-hydroxy-4-ethoxynaphthalene-2,3-dicarboxylate 139a and had the following spectroscopic properties:

IR: ν_{max}; 1735 and 1670 cm^{-1}

^{1}H NMR: 1.47 (t, 3H, OCH$_2$CH$_3$, J = 6.0 Hz), 3.97 (s, 6H, 2 X OCH$_3$), 4.12 (q, 2H, OCH$_2$CH$_3$, J = 6.0 Hz), 7.65 (m, 2H, aromatic), 8.07 (m, 1H, aromatic), 8.47 (m, 1H, aromatic) and 12.13 (s, 1H, ArOH). (Fig. 3).

Anal: Calc. for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30. Found: C, 63.27; H, 5.29%.

HRMS: Calc. for $C_{16}H_{16}O_6$: 304.094; Found: 304.097.

Reaction of 127a with 106 at atmospheric pressure

Compound 127a (1.04 g, 5 m mole) and 106 (1.4 g, 10 m mole) were heated together at 145^{0}C for 5 h under an argon atmosphere. The brown oil was subjected to high vacuum distillation to remove the more volatile starting materials. The product (1.17 g, 76%) was collected as a yellow oil. The oil was crystallized from dry ether and identified as 139a.

Ethylation of 139a

Compound 139a (304 mg, 1 m mole) was dissolved in 20 ml of dry THF, sodium hydride (2 m mole) was added, followed by the addition of 8 m moles of ethyl iodide. The solution was heated in an oil bath at 80^{0}C for 24 h, the solvent was removed, the residue taken up in benzene, and the benzene extract washed with water, dried over sodium sulfate and evaporated. The solid residue (205 mg, 60%) was crystallized from pentane to give material which melted at 87-89°C. It proved to be dimethyl 1,4-diethoxynaphthalene-2,3-dicarboxylate 140a and had the following spectroscopic properties:

IR: ν_{max}; 1735 cm^{-1}

^{1}H NMR: 1.48 (t, 6H, 2 X $OCH_2\underline{CH_3}$, J = 6.0 Hz), 3.88 (s, 6H, 2 X OCH_3), 4.20 (m, 4H, 2 X $O\underline{CH_2}CH_3$), 7.65 and 8.22 (m, 4H, AA'BB', aromatic). (Fig. 4).

Anal. Calc. for $C_{18}H_{20}O_6$: C, 65.09; H, 6.07. Found: C, 65.31; H, 6.21%.

HRMS: Calc. for $C_{18}H_{20}O_6$; 332.125; Found: 332.124.

Reaction of 5,6-dimethoxy-1,1-diethoxyphthalan 127b with 106

In a Carius tube were placed 564 mg (2.1 m mole) of 127b and 298 mg (2.1 m mole) of 106 in 6 ml of chloroform. The tube was cooled and sealed under vacuum, then heated in a furnace for 6 h at 150°C. The tube was cooled, opened and the contents were removed. Evaporation of the solvent yielded an oil that was subjected to high vacuum distillation. The more volatile starting materials were removed and the product (550 mg, 71%) was crystallized from methanol to give dimethyl 6,7-dimethoxy-1-hydroxy-4-ethoxynaphthalene-2,3-dicarboxylate 139b melting at 149-151°C.

IR: ν_{max}; 1735 and 1670 cm^{-1}

^{1}H NMR: 1.47 (t, 3H, $OCH_2\underline{CH_3}$, J = 7.5 Hz), 3.95 (s, 6H, 2 X $O\underline{CH_3}$), 4.03 (s, 6H, 2 X $O\underline{CH_3}$), 4.10 (q, 2H, $O\underline{CH_2}CH_3$, J = 7.5 Hz), 7.30 (s, 1H, aromatic), 7.68 (s, 1H, aromatic) and 12.10 (s, 1H, ArO$\underline{H}$). (Fig. 5).

Anal. Calc. for $C_{18}H_{20}O_8$: C, 59.34; H, 5.35. Found: C, 59.50; H, 5.64%.

HRMS: Calc. for $C_{18}H_{20}O_8$: 364.115; Found: 364.113.

Reaction of 127b with 106 at atmospheric pressure

Compound 127b (1.32 g, 5 m mole) and 106 (1.40 g, 10 m mole) were heated together for 5 h at 155°C under an argon atmosphere. The excess of dienophile was removed under high vacuum distillation. The orange solid was crystallized from methanol to give 1.2 g (67%) of 139b.

Ethylation of 139b

The compound 139b (364 mg, 1 m mole) was ethylated in the same way that 139a was converted to 140a. The resulting product (231 mg, 60%) was crystallized from ether and identified as dimethyl 6,7-dimethoxy-1,4-diethoxynaphthalene-2,3-dicarboxylate. It melted at 152-153°C and had the following spectroscopic properties:

IR: ν_{max}; 1735 cm^{-1}

^{1}H NMR: 1.48 (t, 6H, 2 X $OCH_2\underline{CH_3}$, J = 6.0 Hz), 3.98 (s, 6H, 2 X $O\underline{CH_3}$), 4.03 (s, 6H, 2 X $O\underline{CH_3}$), 4.18 (q, 4H, 2 X $O\underline{CH_2}CH_3$, J = 6.0 Hz) and 7.46 (s, 2H, aromatic). (Fig. 6).

Anal. Calc. for $C_{20}H_{24}O_8$: C, 61.22; H, 6.17. Found: C, 61.03; H, 6.10%.

HRMS: Calc. for $C_{20}H_{24}O_8$: 392.145; Found: 392.147.

Reaction of 127a with ethyl propiolate 165

Ortho ester 127a (1.04 g, 5 m mole) and 165 (835 mg, 8.5 m mole) were heated together for 4 h at 115-120°under an argon atmosphere. The excess of dienophile was then removed by distillation leaving 1.1 g of brown oil that was separated into two components by column chromatography (silica gel for TLC, benzene: hexane = 50:50). The first component (65 mg, 5%) to be eluted proved to be ethyl 1-hydroxy-4-ethoxynaphthalene-2-carboxylate 167. It crystallized from hexane and melted at 99-101°C and had the following spectroscopic properties:

IR: ν_{max}; 1665 cm^{-1} (Fig. 10).

^1H NMR: 1.45 and 1.53 (overlapping t's 6H, 2 X $OCH_2\underline{CH_3}$), 4.18 (q, 2H, $O\underline{CH_2}CH_3$, J = 6.0 Hz), 4.46 (q, 2H, $O\underline{CH_2}CH_3$, J = 6.0 Hz), 7.04 (s, 1H, aromatic), 7.59 (m, 2H, aromatic), 8.33 (m, 2H, aromatic) and 11.70 (s, 1H, ArO$\underline{H}$). (Fig. 12).

Anal. Calc. for $C_{15}H_{16}O_4$: C, 69.23; H, 6.20. Found: C, 68.74; H, 6.28%.

HRMS: Calc. for $C_{15}H_{16}O_4$: 260.104; Found: 260.106.

The second component (355 mg, 27%) eluted from the column was an isomer of the previous compound. It proved to be ethyl 1-hydroxy-4-ethoxynaphthalene-3-carboxylate 166. It melted at 139-141°C after crystallization from acetone-hexane and had the following spectroscopic properties:

IR: ν_{max}; 3610, 3420 and 1720 cm^{-1} (Fig. 9).

^1H NMR: 1.49 and 1.53 (overlapping t's, 6H, 2 X $OCH_2\underline{CH_3}$), 4.13 (q, 2H, $O\underline{CH_2}CH_3$, J = 7.5 Hz), 4.45 (q, 2H, $O\underline{CH_2}CH_3$; J = 7.5 Hz), 5.90 (br.s, 1H, ArO$\underline{H}$), 7.33 (s, 1H, aromatic), 7.59 (m, 2H, aromatic) and 8.21 (m, 2H, aromatic). (Fig. 11).

Anal. Calc. for $C_{15}H_{16}O_4$: C, 69.23; H, 6.20. Found: C, 68.75; H, 6.41%.

HRMS: Calc. for $C_{15}H_{16}O_4$: 260.104; Found: 260.108.

Reaction of 127a with ethyl tetrolate 168

Ortho ester 127a (1.04 g, 5 m mole) and 168 (1.12 g, 10 m mole) were heated for 4 h at 165-170^{0}C under a nitrogen atmosphere. The excess of dienophile was removed by distillation leaving 1.1 g of brown oil that was separated into two components by column chromatography (silica gel for TLC, methylene chloride: petroleum ether = 50:50). The first component eluted (73 mg, 5%) proved to be ethyl 1-hydroxy-3-methyl-4-ethoxynaphthalene-2-carboxylate 170. It crystallized from hexane and melted at 82-84^{0}C and had the following spectroscopic properties:

IR: ν_{max}; 1655 cm^{-1}

^{1}H NMR: 1.45 and 1.48 (overlapping t's, 6H, 2 X $OCH_2\underline{CH_3}$, J = 6.0 Hz), 2.58 (s, 3H, 1 X $\underline{CH_3}$), 3.92 (q, 2H, $O\underline{CH_2}CH_3$, J = 6.0 Hz), 4.47 (q, 2H, $O\underline{CH_2}CH_3$, J = 6.0 Hz), 7.52 (m, 2H, aromatic), 8.00 (m, 1H, aromatic), 8.40 (m, 1H, aromatic) and 12.10 (s, 1H, ArO$\underline{H}$).

Anal. Calc. for $C_{16}H_{18}O_4$: C, 70.13; H, 6.62. Found: C, 70.36; H, 6.43%.

HRMS: Calc. for $C_{16}H_{18}O_4$: 274.120; Found: 274.123.

The second component (657 mg, 48%) eluted from the column was an isomer of the previous compound. It proved to be ethyl 1-hydroxy-2-methyl-4-ethoxynaphthalene-3-carboxylate 169. It melted at 91-92^{0}C after crystallization from hexane and had the following spectroscopic properties:

IR: ν_{max}; 3610, 3380 and 1730 cm^{-1}

^{1}H NMR: 1.40 and 1.43 (overlapping t's, 6H, 2 X $OCH_2\underline{CH_3}$), 2.25 (s, 3H, 1 X $\underline{CH_3}$), 4.08 (q, 2H, $O\underline{CH_2}CH_3$, J = 6.0 Hz), 4.46 (q, 2H, $O\underline{CH_2}CH_3$, J = 6.0 Hz), 5.50 (s, 1H, ArO$\underline{H}$), 7.43 (m, 2H, aromatic) and 8.00 (m, 2H, aromatic).

Anal. Calc. for $C_{16}H_{18}O_4$: C, 70.13; H, 6.62. Found: C, 70.25; H, 6.33%.

HRMS: Calc. for $C_{16}H_{18}O_4$: 274.120; Found: 274.121.

Reaction of <u>127a</u> with ethyl phenylpropiolate <u>171</u>

Ortho ester <u>127a</u> (1.04 g, 5 m mole) and <u>171</u> (1.90 g, 11 m mole) were heated together for 4 h at 165-170°C under an argon atmosphere. The solution was cooled, the excess of dienophile was removed by distillation and the residue (1.8 g) of brown oil was chromotographed on silica gel for TLC using benzene: hexane = 50:50 as eluant. The first fraction (437 mg, 28%) was crystallized from hexane and melted at 84-85°C. It proved to be ethyl 1-hydroxy-3-phenyl-4-ethoxynaphthalene-2-carboxylate <u>173</u> and had the following spectroscopic properties:

IR: ν_{max}; 1650 cm^{-1}

^{1}H NMR: 0.73 (t, 3H, $OCH_2\underline{CH_3}$, J = 6.0 Hz), 1.03 (t, 3H, $OCH_2\underline{CH_3}$, J = 6.0 Hz), 3.55 (q, 2H, $O\underline{CH_2}CH_3$, J = 6.0 Hz), 3.97 (q, 2H, $O\underline{CH_2}CH_3$, J = 6.0 Hz), 7.35 (s, 5H, phenyl), 7.40-7.90 (m, 2H, aromatic), 8.10 (m, 1H, aromatic), 8.47 (m, 1H, aromatic) and 12.10 (s, 1H, ArO$\underline{H}$).

Anal. Calc. for $C_{21}H_{20}O_4$: C, 74.94; H, 5.99; Found: C, 74.86; H, 5.99%.

HRMS: Calc. for $C_{21}H_{20}O_4$: 336.136; Found: 336.134.

The second fraction from the column (576 mg, 34%) was an oil that failed to crystallize. The oil was purified by distillation in a Kugelrohr apparatus. It proved to be ethyl 1-hydroxy-2-phenyl-4-ethoxynaphthalene-3-carboxylate 172 which had the following properties: bp 100°C at 0.05 mm Hg.

IR (neat): ν_{max}; 3530 and 1730 cm^{-1}

^{1}H NMR: 0.93 (t, 3H, $OCH_2\underline{CH_3}$, J = 6.0 Hz), 1.45 (t, 3H, $OCH_2\underline{CH_3}$, J = 6.0 Hz), 4.00 and 4.17 (overlapping q's, 2 X $O\underline{CH_2}CH_3$), 5.43 (br.s, 1H, $ArO\underline{H}$), 7.10-8.40 (m, 4H, aromatic) and 7.42 (s, 5H, phenyl).

Anal. Calc. for $C_{21}H_{20}O_4$: C, 74.86; H, 5.99; Found: C, 74.80; H, 6.01%.

HRMS: Calc. for $C_{21}H_{20}O_4$: 336.136; Found: 336.134.

Reaction of 127a with 1,4-hydroquinone 163

Ortho ester 127a (1.04 g, 5 m mole) and 163 (550 mg, 5 m mole) were heated together for 2 h at 165°C under a nitrogen atmosphere. The red oil was treated with methylene chloride to precipitate 123 mg of 163. The solvent was evaporated to dryness and the residue (1.1 g) was subjected to high vacuum distillation to yield 385 mg of 127a, 72 mg of 163 and 598 mg of an orange solid which was purified by preparative TLC (silica gel, methylene chloride) and crystallized from acetone-hexane. It melted at 113-114°C. It was identified as 2-carboethoxybenzyl 4-hydroxyphenyl ether 164 and had the following spectroscopic properties:

IR: ν_{max}; 3550, 3420 and 1710 cm^{-1} (Fig. 8).

^{1}H NMR: 1.35 (t, 3H, $OCH_2\underline{CH_3}$, J = 7.5 Hz), 4.36 (q, 2H, $O\underline{CH_2}CH_3$, J = 7.5 Hz), 5.16 (s, 1H, ArO$\underline{H}$, collapses with added D_2O), 5.40 (s, 2H, Ar$\underline{CH_2}$), 6.78 (m, 4H, hydroquinone), 7.50 (m, 3H, aromatic), and 8.03 (m, 1H, aromatic). (Fig. 7).

Anal. Calc. for $C_{16}H_{16}O_4$: C, 70.64; H, 5.92. Found: C, 70.66; H, 6.14%.

HRMS: Calc. for $C_{16}H_{16}O_4$: 272.103; Found: 272.104.

Attempt to brominate 127a with N-bromosuccinimide (NBS)

Ortho ester 127a (2.08 g, 10 m mole) and NBS (1.78 g 10 m mole) were refluxed in 26 ml of dry carbon tetrachloride for 30 minutes under the illumination of a 100 watt light bulb. The end of the reaction was indicated by disappearance of NBS from the bottom and the accumulation of succinimide at the top of the reaction mixture. The succinimide was removed by filtration. The filtrate was concentrated to give an oil (2.3 g) which showed two molecular ions in the mass spectrum. The first, tentatively assigned to 158 contained the expected doublet for Br at m/e 242 and at m/e 244 in a ratio of ca 1:1. The second molecular ion was assigned to 159 at m/e 222. The infrared of the mixture showed a carbonyl band at 1730 cm^{-1}. The ^{1}H NMR spectrum also indicated that the product was a mixture.

Attempt to generate 136 at low temperature

To a suspension of 132a (2.5 g, 10 m mole) in methylene chloride at -40°C was added a solution of N-methylpiperidine (1 g, 10 m mole). During the addition gas was involved and the salt went into the solution. After 20 min., the reaction solution was washed with brine, and the organic layer was evaporated to dryness to give a solid identified as phthalide.

Reaction of 127a with diethyl maleate 174 in a sealed tube

Ortho ester 127a (344 mg, 2 m mole), alkene 174 (419 mg, 2 m mole) and chloroform (2 ml) were placed in a Carius tube. The tube was cooled and sealed under vacuum. The mixture was heated in a furnace for 72 h at 170^{o}C. The tube was cooled, opened and the contents were removed. Upon evaporation of the solvent the yellow oil obtained on vacuum distillation was subjected to preparative TLC (silica gel, benzene) to give two fractions. The first fraction (55 mg, 10%) was a yellow oil that crystallized from hexane melting at 54-56^{o}C. It was identified as diethyl 1-hydroxynaphthalene-2,3-dicarboxylate 180.

IR: ν_{max}; 1730 and 1665 cm^{-1}

^{1}H NMR: 1.48 (t, 6H, 2 x $OCH_2\underline{CH_3}$, J = 6.0 Hz), 4.40 and 4.45 (overlapping q's, 4H, 2 X $O\underline{CH_2}CH_3$), 7.45 (s, 1H, aromatic), 7.68 (m, 3H, aromatic), 8.43 (m, 1H, aromatic) and 12.10 (s, 1H, ArO$\underline{H}$). (Fig. 13).

Anal. Calc. for $C_{16}H_{16}O_5$: C, 66.66; H, 5.55; Found: C, 66.07; H, 5.36%.

HRMS: Calc. for $C_{16}H_{16}O_5$: 288.099; Found: 288.099.

The second fraction (214 mg, 30%) was a yellow oil that failed to crystallize. The oil was purified by distillation in a Kugelrohr apparatus and proved to be diethyl 1-ethoxynaphthalene-2,3-dicarboxylate 178.

IR (neat liquid): ν_{max}; 1730 cm^{-1}

^{1}H NMR: 1.37, 1.38 and 1.43 (overlapping t's, 9H, 3 X $OCH_2\underline{CH_3}$), 4.20, 4.38 and 4.47 (overlapping q's, 6H, 3 X $O\underline{CH_2}CH_3$), 7.58 (m, 2H, aromatic), 7.92 (m, 1H, aromatic), 8.12 (m, 1H, aromatic) and 8.32 (s, 1H, aromatic). (Fig. 14).

Anal. Calc. for $C_{18}H_{20}O_5$: C, 68.35; H, 6.32. Found: C, 68.29; H, 6.39%.

HRMS: Calc. for $C_{18}H_{20}O_5$: 316.131; Found: 316.132.

Ethylation of 180 (56)

A mixture of 180 (97 mg, 0.3 m mole), ethyl iodide (2.5 g, 1.6 m mole) and potassium carbonate (2.5 g, 18 m mole) in 20 ml of anhydrous acetone was refluxed for 50 h. The acetone was evaporated and the residue was taken up in benzene. The benzene was washed with 5% aqueous potassium hydroxide dried over sodium sulfate, and evaporated to give a yellow oil (76.5 mg, 72%) whose spectroscopic properties were similar to those reported for 178.

Reaction of 127a with 174 at atmospheric pressure

Ortho ester 127a (1.04 g, 5 m mole) and 174 (1.72 g, 10 m mole) were heated together for 6 h at 165-170^{0}C under an atmosphere of argon. The excess of dienophile was removed by distillation under vacuum giving 1.8 g of yellow oily residue. Column chromatography of the oil (silica gel for TLC, benzene: acetone = 95:5) yielded three fractions. The first fraction (688 mg, 43%) was the already reported 178; the second fraction (500 mg) proved to be a mixture of two components that was separated by preparative TLC using the same conditions as in column chromatography. This was comprised of 76 mg (5%) of the compound present in the first fraction and 300 mg (18%) of a second component (larger Rf) that proved to be diethyl 1-hydroxy-4-ethoxy-1,2-dihydronaphthalene 177a.

IR (neat liquid): ν_{max}: 3480 and 1730 cm^{-1}

^{1}H NMR: 105 (t, 3H, $OCH_2\underline{CH_3}$, J = 6.0 Hz), 1.38 and 1.42 (overlapping t's, 6H, 2 X $O\underline{CH_2}CH_3$), 4.04 (m, 5H, 2 X $O\underline{CH_2}CH_3$ and H-2), 4.31 (q, 2H, $O\underline{CH_2}CH_3$, J = 6.0 Hz), 5.08 (d,d, 1H, H-1, J = 6.0 Hz, with added D_2O this signal collapses to a doublet, J = 6.0 Hz), and 7.20-7.80 (m, 4H aromatic). (Fig. 15).

^{1}H NMR (DMSO-d_6): 0.95-1.40 (m, 9H, 3 X $OCH_2\underline{CH_3}$) 3.70-4.28 (m, 7H, 3 X $O\underline{CH_2}CH_3$ and H-2), 5.16 (t, 1H, H-1, J = 6.0 Hz, with added D_2O this signal collapses to a doublet J = 6.0 Hz), 5.80 (d, 1H, $CO\underline{H}$, J = 6.0 Hz, this signal disappears in added D_2O) and 7.36-7.75 (m, 4H, aromatic). (Fig. 15b).

HRMS: Calc. for $C_{18}H_{22}O_6$: 334.142; Found: 334.146.

The third fraction (568 mg, 34%) isolated from the column proved to be an isomer, 177b, of the previous substance. It was also obtained as an oil and had the following physical properties:

IR (neat liquid): ν_{max}; 3480 and 1730 cm^{-1}

^{1}H NMR: 1.13, 1.30 and 1.38 (overlapping t's, 9H, 3 X $OCH_2\underline{CH_3}$), 2.18 (b.s, 1H, $CO\underline{H}$, disappears in added D_2O), 4.05 (m, 5H, 2 X $O\underline{CH_2}CH_3$ and H-2), 5.00 (d, 1H, H-1, J = 4.5 Hz) and 7.30-7.80 (m, 4H, aromatic). (Fig. 16).

HRMS: Calc. for $C_{18}H_{22}O_6$: 334.142; Found: 334.140.

When the reaction was repeated under the same conditions as above except that a different batch of silica was used, two compounds were isolated. The first fraction (238 mg, 15%) identified as 178 and the second fraction (970 mg, 63%) was also an oil and identified as 179.

IR (neat liquid): ν_{max}: 3480, 1735 and 1665 cm^{-1}.

^{1}H NMR: 1.03-1.43 (m, 6H, 2 X OCH_2CH_3), 2.80 (br.s, 1H, COH), 3.90-4.36 (m, 5H, 2 X OCH_2CH_3 and H-2), 5.10 (b.s, 1H, H-1), 7.43-8.10 (m, 4H, aromatic) and 12.80 (s, 1H, COH).

HRMS Calc. for $C_{16}H_{18}O_6$: 306.107; Found: 306.110.

Conversion of 177a, 177b and 179 to 180

In each case, the compound was refluxed in benzene in the presence of catalytic quantities of p-toluenesulsufonic acid for 30 min. The solution was washed with brine and dried over sodium sulfate to give 180 in 92-95% yield, identified by its spectroscopic properties.

Reaction of 127a with maleic anhydride 70

Ortho ester 127a (1.04 g, 5 m mole) and 70 (500 mg, 5 m mole) were heated together for 10 min. at 165°C under a nitrogen atmosphere. The solution was cooled and the solid residue was crystallized from acetone to give 668 mg (56%) of white crystals that melted at 170-172°C and were identified as 1-ethoxynaphthalene-2,3-dicarboxylic acid anhydride.

IR: ν_{max}; 1845 and 1785 cm^{-1}.

^{1}H NMR: 1.55 (t, 3H, OCH_2CH_3, J = 7.5 Hz), 4.82 (q, 2H, OCH_2CH_3, J = 7.5 Hz), 7.50-8.20 (m, 3H, aromatic), 8.07 (s, 1H, aromatic) and 8.47 (m, 1H, aromatic). (Fig. 17).

Anal. Calc. for $C_{14}H_{10}O_4$: C, 69.42; H, 4.16. Found: C, 68.98; H, 4.17%.

HRMS: Calc. for $C_{14}H_{10}O_4$: 270.057; Found: 270.054.

Reaction of 127a with 1,4-benzoquinone 182

Ortho ester 127a (1.04 g, 5 m mole) and 182 (540 mg, 5.5 m mole) were heated together for 45 min. at 146-148°C under an argon atmosphere. The brown oil was cooled, dissolved in methylene chloride and filtered through alumina (neutral) to give 380 mg (29%) of white crystals that after crystallization from ethanol melted at 121-122°C. The compound proved to be ethyl 2-[(1'R*, 6'S*, 7'S*)-2',5'-dioxo-3'-norcaren-7'-yl] benzoate 183 and had the following spectroscopic properties:

IR: ν_{max}; 1715 and 1685 cm^{-1}

^1H NMR: 1.37 (t, 3H, OCH_2CH_3, J = 7.5 Hz), 2.83 (d, 2H, H-1' and H-6', J = 5.4 Hz), 4.02 (t, 1H, H-7', J = 5.4 Hz), 4.38 (q, 2H, OCH_2CH_3, J = 7.5 Hz), 6.60 (s, 2H, H-3' and H-4'), 7.40 (m, 3H, aromatic) and 8.05 (m, 1H, aromatic). (Fig. 18).

Anal. Calc. for $C_{16}H_{14}O_4$: C, 71.14; H, 5.22. Found: C, 70.87; H, 5.28%.

HRMS: Calc. for $C_{16}H_{14}O_4$: 270.089; Found: 270.090.

Reaction of 127a with 1,4-naphthoquinone 66

Ortho ester (1.04 g, 5 m mole) and 66 (790 mg, 5 m mole) were heated together at 140°C for 20 min. under an argon atmosphere. The resulting brown oil (1.6 g) was subjected to column chromatography (silica gel, 160 g) using methylene chloride as eluant. The first fraction (450 mg, 28%) was purified on a Lobar reverse phase column (CH_3CN-H_2O = 7:3) and the product crystallized from pentane and melted 82-83^{0}C. It proved to be 2-(2'-carboethoxybenzyl)-1,4-naphthoquinone 187 and had the following spectroscopic properties:

IR: ν_{max}; 1725 and 1675 cm^{-1}

^{1}H NMR: 1.28 (t, 3H, $OCH_2\underline{CH_3}$, J = 6.0 Hz), 4.26 (q, 2H, $OCH_2\underline{CH_3}$, J = 6.0 Hz), 4.30 (s, 2H, H-11), 6.28 (t, 1H, H-3), 7.41 (m, 3H, aromatic), 7.73 (m, 2H, aromatic), and 8.10 (m, 3H, aromatic). (Fig. 22).

Anal. Calc. for $C_{20}H_{16}O_4$: C, 75.03; H, 5.03: Found: C, 75.07; H, 5.20%.

HRMS: Calc. for $C_{20}H_{16}O_4$: 320.104; Found: 320.104

The second fraction from the column was filtered through neutral alumina to remove coloured impurities and crystallized from ether to give white crystals that melted at 126-127^{0}C. It was identified as ethyl 2-[(1'R*, 1'aS, 7'aR)-1'a,2',7',7a'-tetrahydro-2',7'-dioxo-1H-cyclopropa [b] naphthalen-1'-yl] benzoate 186.

IR: ν_{max}; 1725 and 1685 cm^{-1}

^{1}H NMR: 1.28 (t, 3H, $OCH_2\underline{CH_3}$, J = 7.0 Hz), 3.01 (d, 2H, H-1'a, and H-7'a, J = 5.3 Hz), 3.85 (t, 1H, H-1', J = 5.3 Hz), 4.29 (q, 2H, $\underline{OCH_2}CH_3$, J = 7.0 Hz) and 7.20-8.20 (m, 8H, aromatic). (Fig. 21)

Anal. Calc. for $C_{20}H_{16}O_4$: C, 75.06; H, 5.03; Found: C, 74.74; H, 5.30%.

HRMS: Calc. for $C_{20}H_{16}O_4$: 320.104; Found: 320.104.

Reaction of 127b with 1,4-benzoquinone 182

Ortho ester 127b (1.3 g, 5 m mole) and 182 (540 mg, 5.5 m mole) were heated together for 10 min. at 155^{0}C under an argon atmosphere. The dark oil was cooled, dissolved in methylene chloride and filtered through neutral alumina to give yellow crystals that were crystallized from benzene-pentane (800 mg, 42%) and melted at 191-192°. The compound was identified as ethyl 4,5-dimethoxy-2-[(1'R*, 6'S*, 7'S*)-2',5'-dioxo-3'-norcaren-7'-yl] benzoate 184 and had the following spectroscopic properties:

IR: ν_{max}; 1710 and 1785 cm^{-1}

^1H NMR: 1.34 (t, 3H, $OCH_2\underline{CH_3}$, J = 7.5 Hz), 2.77 (d, 2H, H-1' and H-6', J = 5.3 Hz), 3.97 (s, 6H, 2 X $\underline{OCH_3}$), 4.02 (overlapping t, 1H, H-7', J = 5.3 Hz), 4.32 (q, 2H, $\underline{OCH_2}CH_3$, J = 7.5 Hz), 6.55 (s, 2H, H-3' and H-4'), 6.60 (s, 1H, aromatic) and 7.35 (s, 1H, aromatic). (Fig. 19).

Anal. Calc. for $C_{18}H_{18}O_6$: C, 65.45; H, 5.45. Found: C, 65.14; H, 5.60%.

HRMS Calc. for $C_{18}H_{18}O_6$: 330.110; Found: 330.109.

The mother liquor was evaporated to dryness and the residue (10 mg, 0.5%) was crystallized from ether. The separated solid melted at 115-116°C. It proved to be ethyl 4,5-dimethoxy-[(1'R*, 6'R*, 7'S*)-2',5'-dioxo-3'-norcaren-7'-yl] benzoate 185.

IR: ν_{max}; 1680 and 1715 cm^{-1}

^1H NMR: 1.41 (t, 3H, $OCH_2\underline{CH_3}$, J = 7.5 Hz), 2.87 (d, 2H, H-1' and H-6', J = 9.0 Hz), 3.55 (t, 1H, H-7', J = 9.0 Hz), 3.80 (s, 3H, $\underline{OCH_3}$), 3.87 (s, 3H, $\underline{OCH_3}$), 4.30 (q, 2H, $\underline{OCH_2}CH_3$, J = 7.5 Hz), 6.1 H (s, 2H, H-3' and H-4'), 6.64 (s, 1H, aromatic) and 7.37 (s, 1H, aromatic). (Fig. 20).

Anal. Calc. for $C_{18}H_{18}O_6$: C, 65.48; H, 5.60. Found C, 65.07; H, 5.65%.

Reaction of 127b with 1,4-naphthoquinone 66

Ortho ester 127b (1.3 g, 5 m mole) and 66 (790 mg, 5 m mole) were heated together for 10 min. at 150°C under an argon atmosphere. The dark oily product was filtered through neutral alumina to give a brown oil (1.4 g) that showed three spots on TLC (silica gel). Crystallization of the oil from acetone-hexane yielded 377 mg (20%) of ethyl 4,5-dimethoxy-2-[(1'R*,1'aS,7'aR*)-1'a,2',7',7'a-tetrahydro-2',7'-dioxo-1H-cyclopropa [b] naphthalen-1'-yl] benzoate 188, it melted at 151-152°C and had the following spectroscopic properties:

IR: ν_{max}; 1710 and 1680 cm^{-1}

^1H NMR: 1.26 (t, 3H, $OCH_2\underline{CH_3}$, J = 7.5 Hz), 2.96 (d, 2H, H-1'a and H-7'a, J = 5.3 Hz), 3.83 (t, 1H, H-1', J = 5.3 Hz), 3.90 (s, 3H, $O\underline{CH_3}$), 3.96 (s, 3H, $O\underline{CH_3}$), 4.23 (q, 2H, $O\underline{CH_2}CH_3$, J = 7.5 Hz), 6.68 (s, 1H, aromatic), 7.50 (s, 1H, aromatic), 7.75 (m, 2H, aromatic) and 8.06 (m, 2H, aromatic). (Fig. 23).

Anal. Calc. for $C_{22}H_{20}O_6$: C, 69.53; H, 5.30. Found C, 69.73; H, 5.54%.

HRMS: Calc. for $C_{22}H_{20}O_6$: 380.125; Found: 380.124.

The mother liquors were evaporated to dryness and the residue was subjected to column chromatography (silica gel, 100 g). Starting materials, 64 mg of 1,4-naphthoquinone and 73 mg of 5,6-dimethoxyphthalide were eluted with methylene chloride, and products (856 mg) with methylenechloride-ether (50:50). Recrystallization of the mixture (856 mg) from acetone-hexane gave 229 mg (12%) of the compound previously described. The mother liquor from this crystallization was removed and the residue (627 mg) showed two spots on TLC (reversed phase, acetonitrile-water = 60:40). A portion of the mixture (3 X 10 mg) was subjected to Lobar reversed phase chromatography using acetonitrile-water (60:40) as eluant. The first fraction (15 mg, 50%) was crystallized from acetone-pentane and melted 131-133^{0}C. It proved to be ethyl 4,5-dimethoxy-2-[(1'R*,1'aR*,7'aS*)-1'a,2',7',7'a-tetrahydro-2',7'-dioxo-1H -cyclopropa [b]naphthalene-1'-yl] benzoate 189 and had the following spectroscopic properties:

IR: ν_{max}; 1710 and 1675 cm^{-1}

^{1}H NMR: 1.45 (t, 3H, $OCH_2\underline{CH_3}$, J = 7.5 Hz), 3.10 (d, 2H, H-1'a and H-7'a, J = 9.8 Hz), 3.70 (overlapping t, 1H, H-1, J = 9.8 Hz), 3.70 (s, 6H, 2 X $O\underline{CH_3}$), 4.36 (q, 2H, $O\underline{CH_2}CH_3$, J = 7.5 Hz), 6.68 (s, 1H, aromatic), 7.08 (s, 1H, aromatic), 7.41 (m, 2H, aromatic) and 7.71 (m, 2H, aromatic). (Fig. 24).

Anal. Calc. for $C_{22}H_{20}O_6$: C, 69.53; H, 5.30. Found: C, 69.06; H, 5.52%.

HRMS: Calc. for $C_{22}H_{20}O_6$: 380.125; Found: 380.126.

The second fraction (10 mg, 33%) showed spectroscopic properties similar to those of 188.

Attempts to react 127a with cyclooctene or 1-phenyl-1-propyne

The reactions were carried out in sealed NMR tubes using $CDCl_3$ or DMSO-d_6 as solvent. In each case equivalent amounts of 127a with cyclooctene or 1-phenyl-1-propyne were used. The solutions were heated in an oil bath at temperatures over the range 120-190^{0}C over a 10 h period. The tubes were examined periodically by NMR but no reaction was found to occur.

SUMMARY

A new reaction between phthalide ortho esters with a series of dienophiles has been studied. Thus, treatment of 1,1-diethoxyphthalan or 5,6-dimethoxy-1,1-diethoxyphthalan with dimethyl acetylenedicarboxylate afforded tetrasubstituted naphthalenes in yields of 65-70%. The regiochemistry of the cycloadditions with unsymmetrical acetylenes was studied and it was found that "ortho adducts" were found as major products.

When the study of the reactions of phthalide ortho esters was extended to activated alkenes, such as diethyl maleate, a mixture of tetrasubstituted 1,2-dihydronaphthalenes and a trisubstituted naphthalene was obtained. The mixture of tetrasubstituted 1,2-dihydronaphthalenes was converted into a disubstituted naphthol by dehydration and hydrolysis under acidic conditions. Maleic anhydride was also used as dienophile and one product was isolated from the reaction.

In the case of the treatment of phthalide ortho esters with quinones, it was found that they reacted in an abnormal fashion to give, in most cases, p-homoquinones.

The structures of the compounds prepared in this study the majority of which were new compounds, were established on the basis of their spectroscopic properties. Infrared, ^{1}H NMR and ^{13}C NMR were used extensively to distinguish between configurational isomers and to determine the position of the functional groups in the molecules.

The formation of the compounds prepared by the reactions

of phthalide ortho esters with dienophiles has been rationalized in terms of a mechanism that involves 1-ethoxyisobenzofurans as intermediates. It has been proposed that the intermediate, unstable adducts from the cycloaddition with acetylenes or alkenes undergo C-O bond cleavage to give zwitterions that later collapse to the products. In the case of the adducts with quinones it is postulated that they undergo simultaneous C-C bond cleavage and enolization followed by internal nucleophilic attack to give the p-homoquinones.

Finally, the method described in this thesis for the preparation of polysubstituted naphthalenes has several advantages. The starting materials are readily available, the reaction is regioselective and leads in a single step to the products in relatively good yield. In the case of the synthesis of p-homoquinones, this method provides a new route to this group of compounds that is short and gives yields that are comparable to those obtained from the standard procedures.

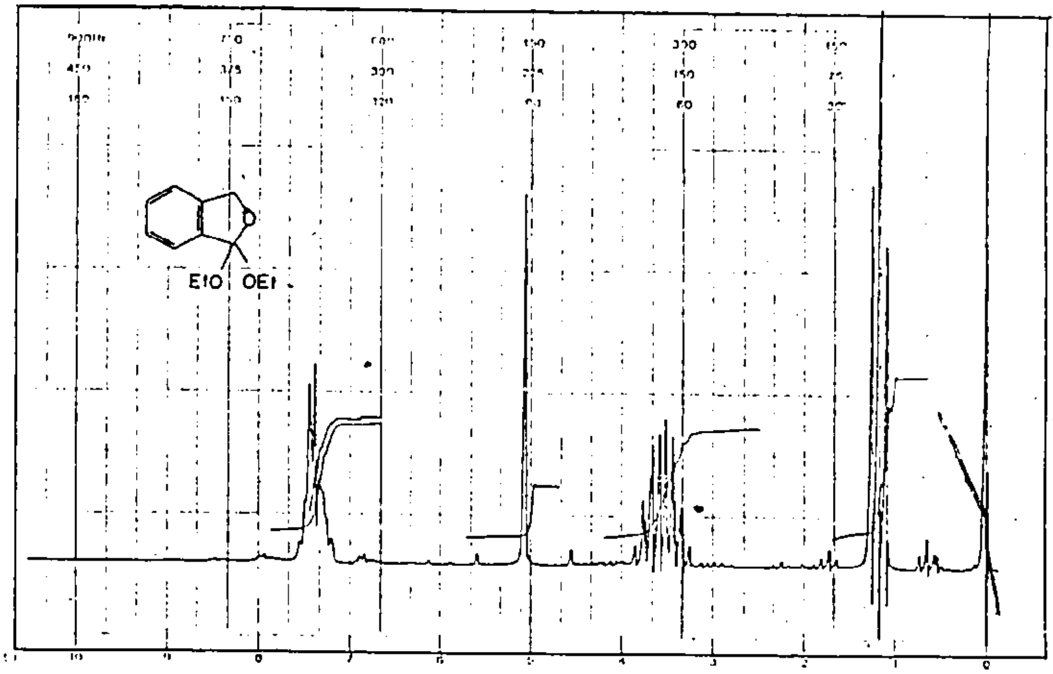


FIGURE 1. ^{1}H NMR spectrum of ortho ester 127a.

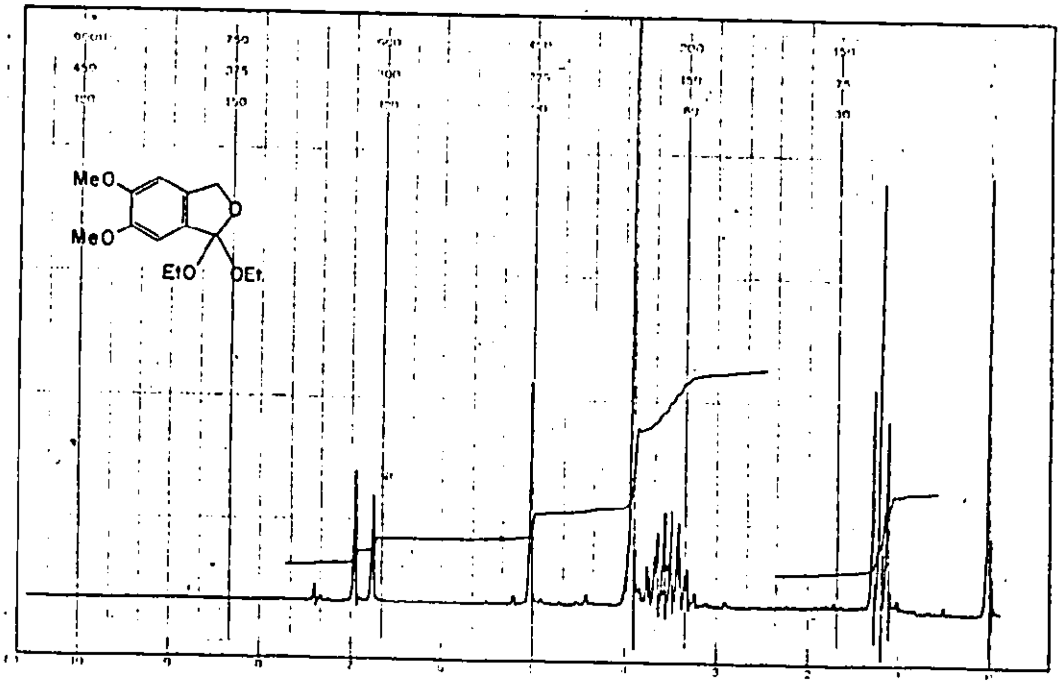


FIGURE 2. ^{1}H NMR spectrum of ortho ester 127b.

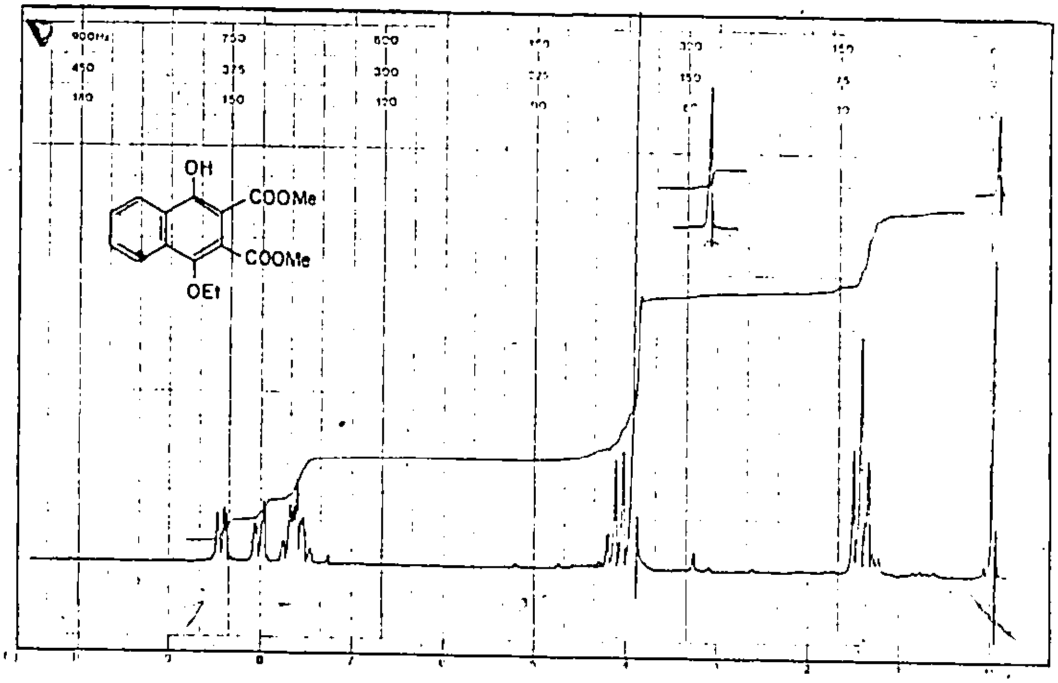


FIGURE 3. ^{1}H NMR spectrum of naphthalene 139a.

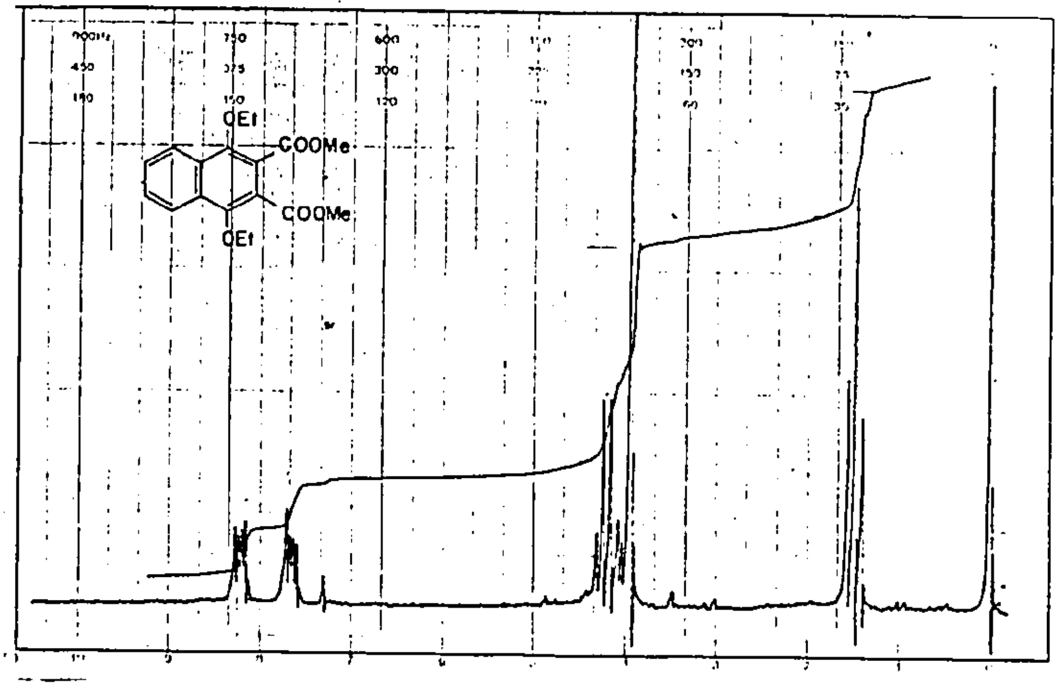


FIGURE 4. ^{1}H NMR spectrum of naphthalene 140a.

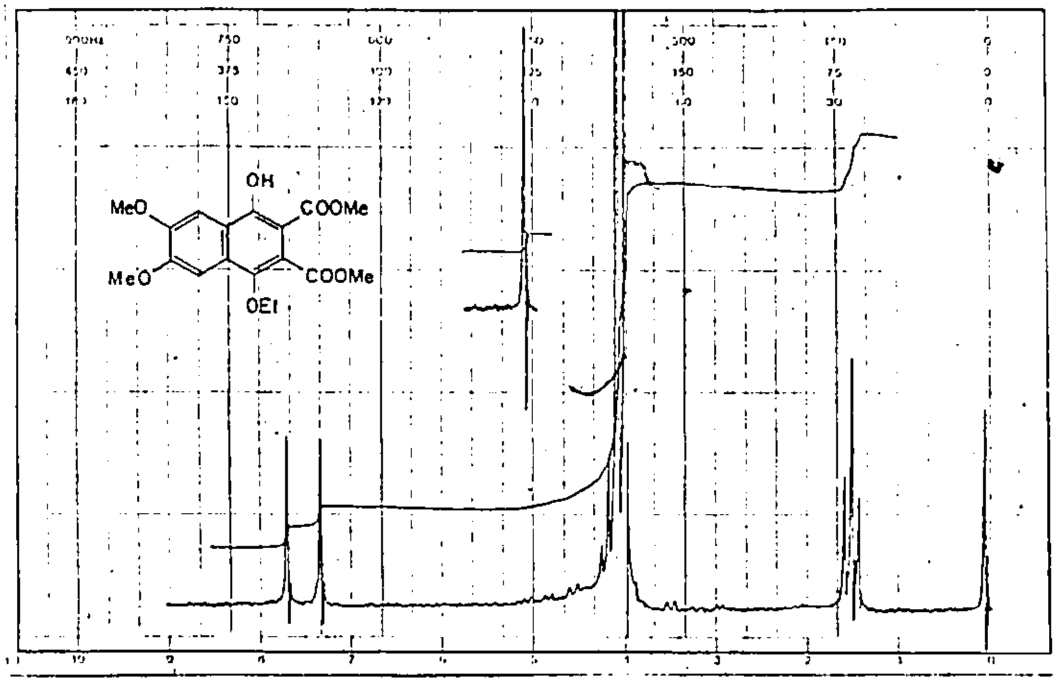


FIGURE 5. ^{1}H NMR spectrum of naphthalene 139b.

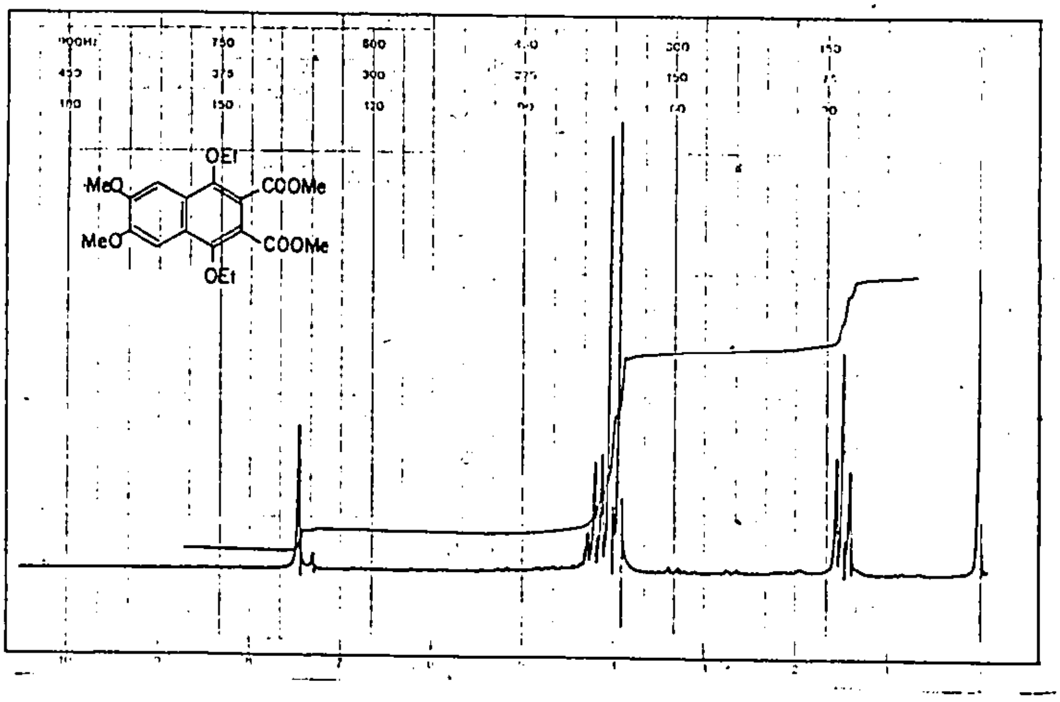


FIGURE 6. ^{1}H NMR spectrum of naphthalene 140b.

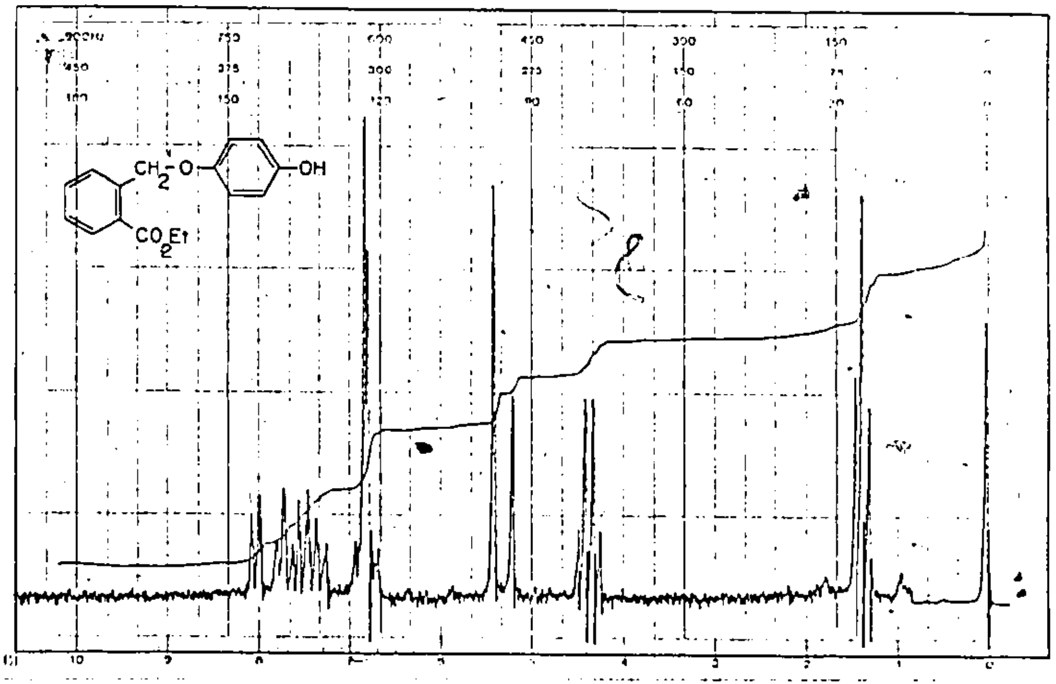


FIGURE 7. ^{1}H NMR spectrum of <u>164</u>.

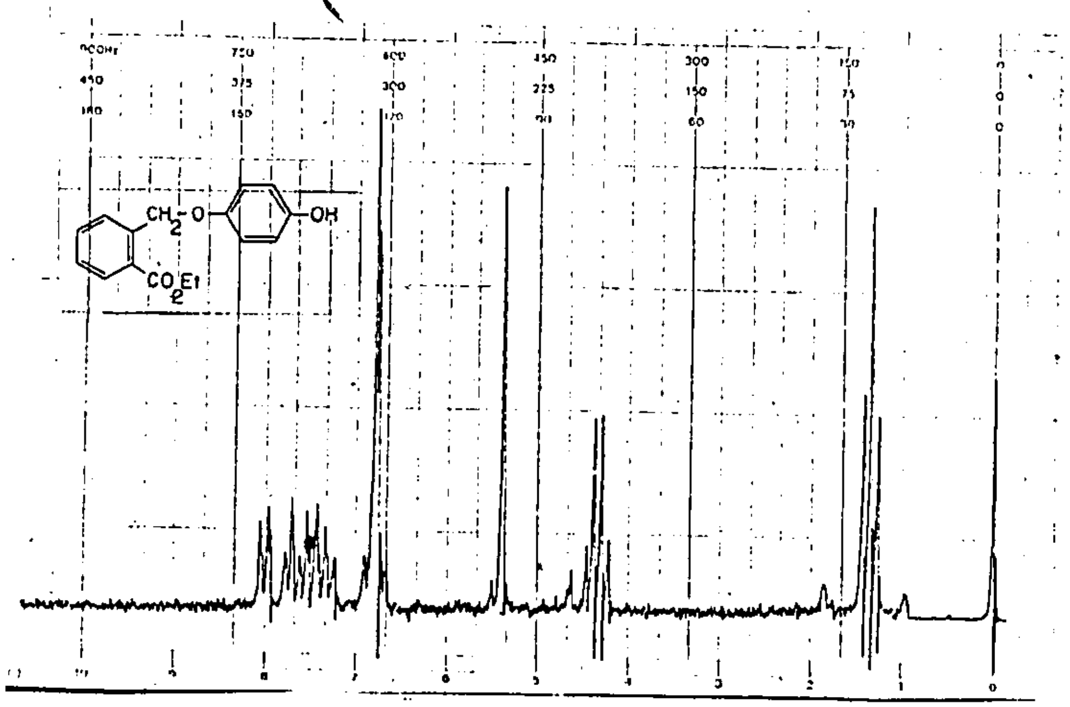


FIGURE 7a. ^{1}H NMR spectrum of <u>164</u> + D_2O.

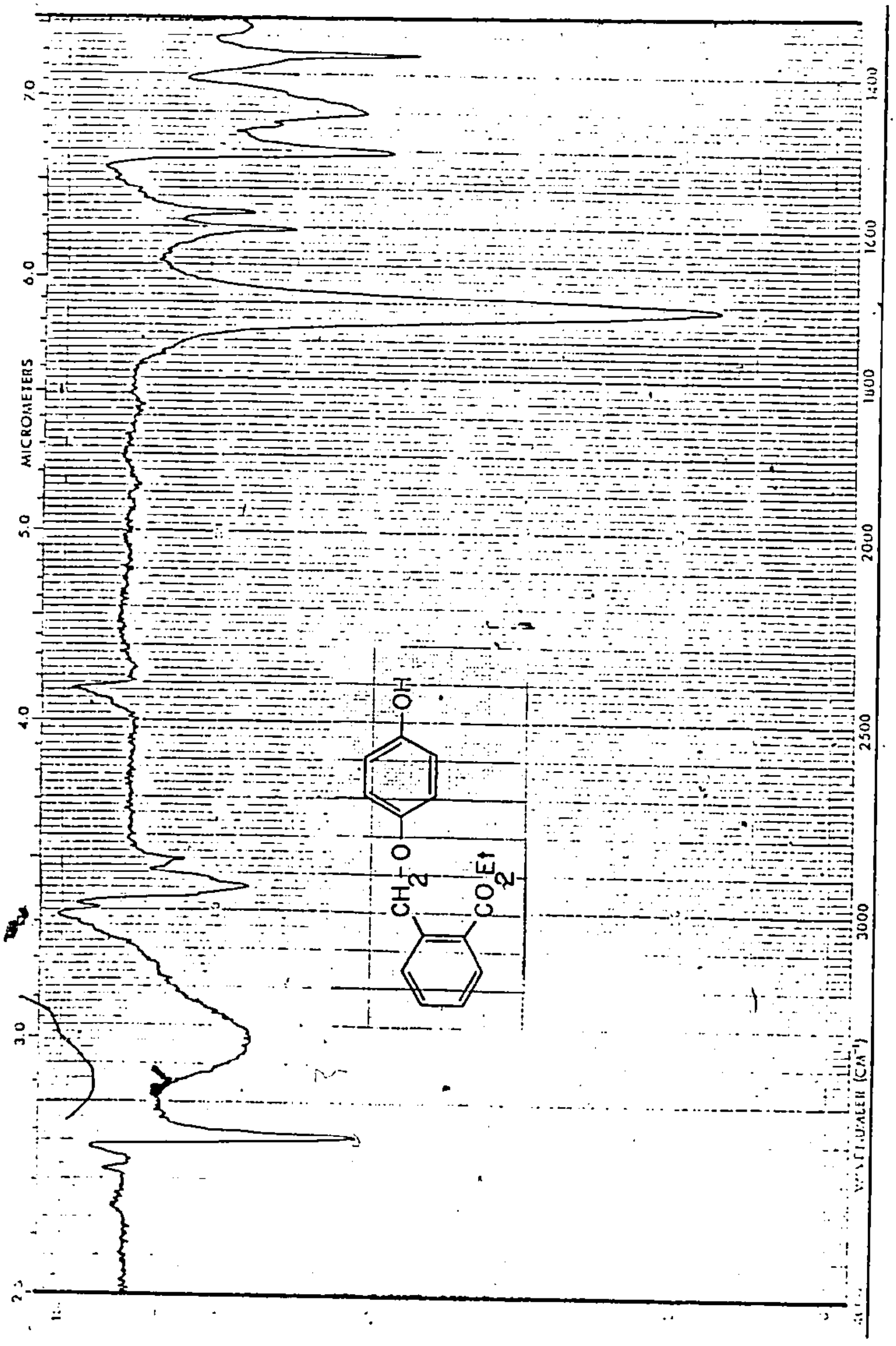


FIGURE 8. IR spectrum of 164.

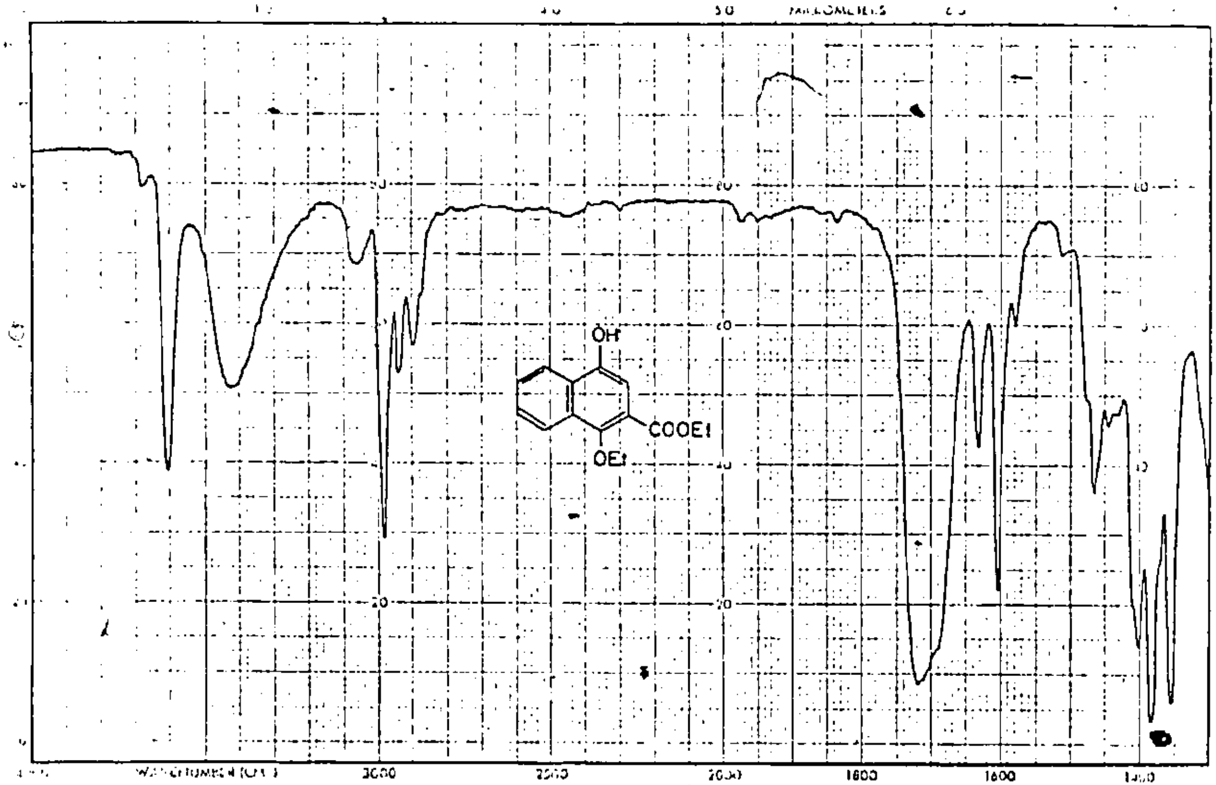


FIGURE 9. IR spectrum of naphthalene 166.

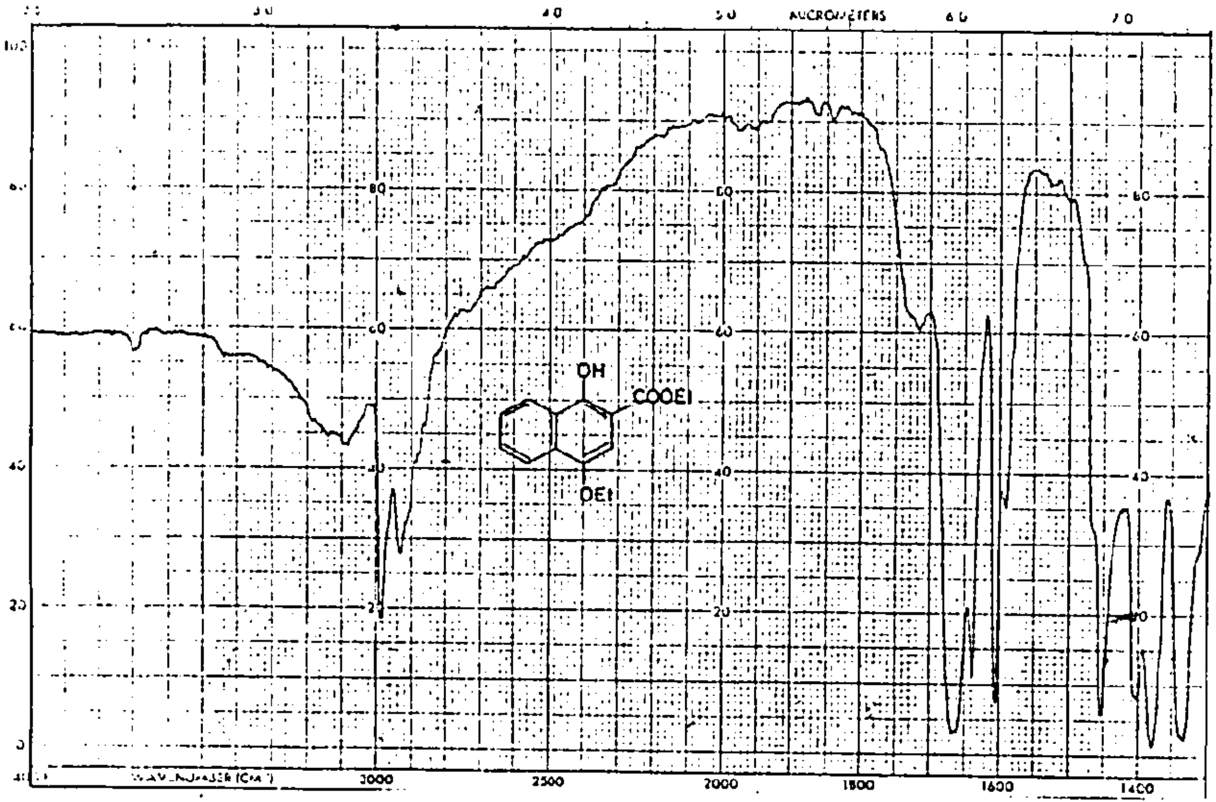


FIGURE 10. IR spectrum of naphthalene 167.

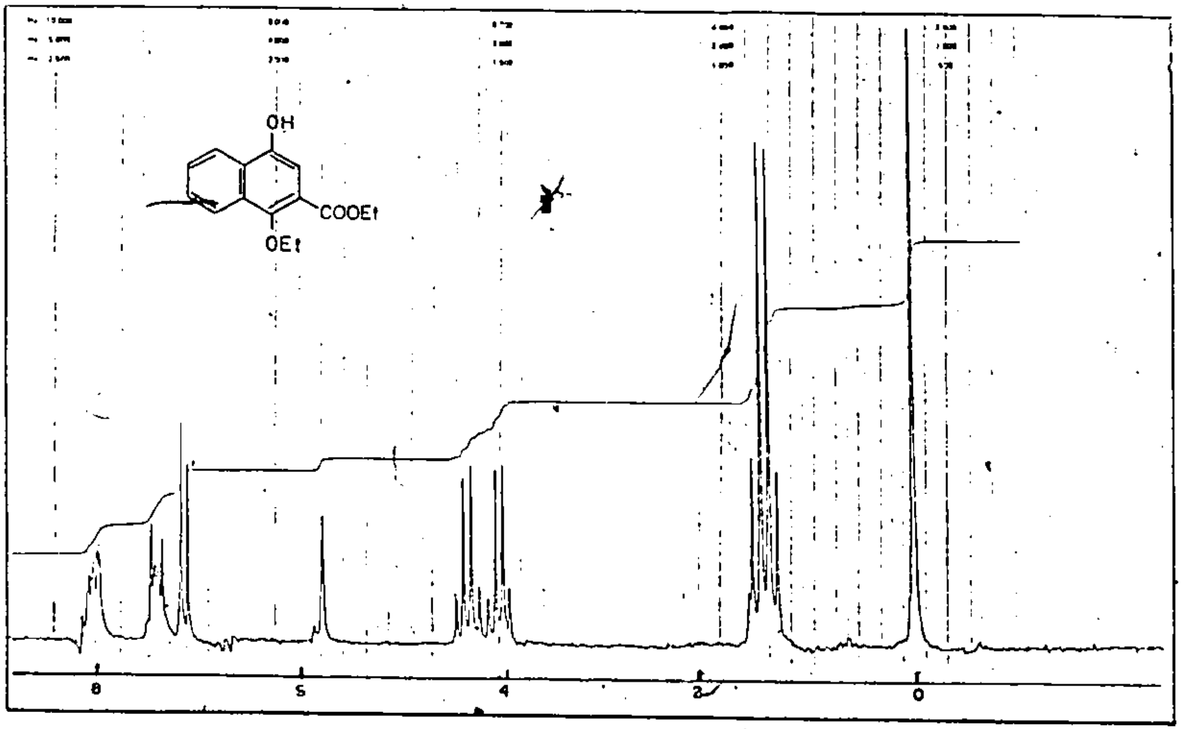


FIGURE 11. ^{1}H NMR spectrum of naphthalene <u>166</u>.

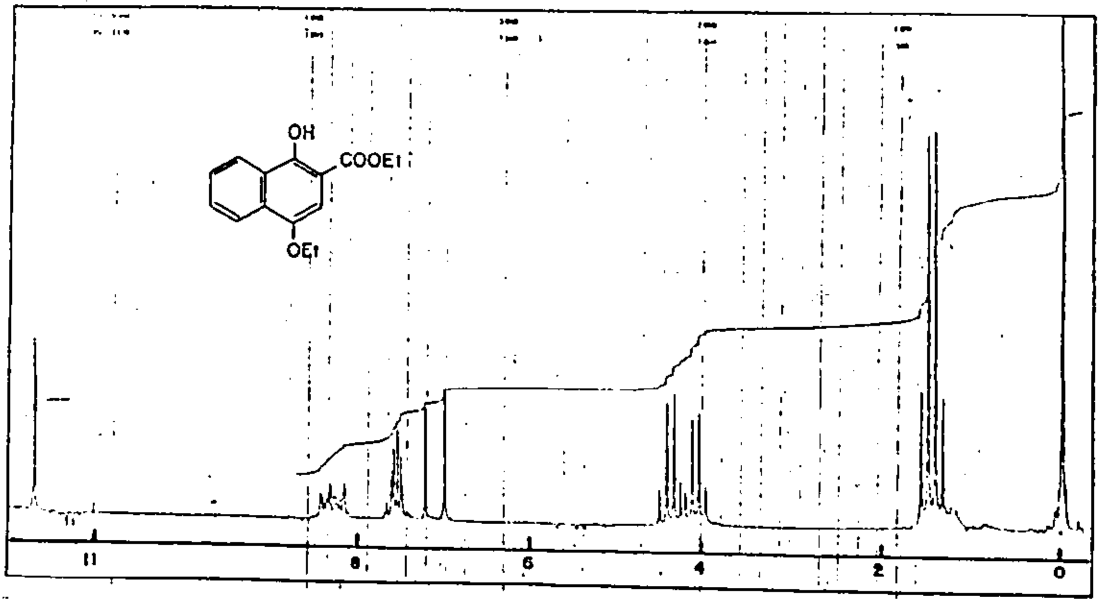


FIGURE 12. ^{1}H NMR spectrum of naphthalene <u>167</u>.

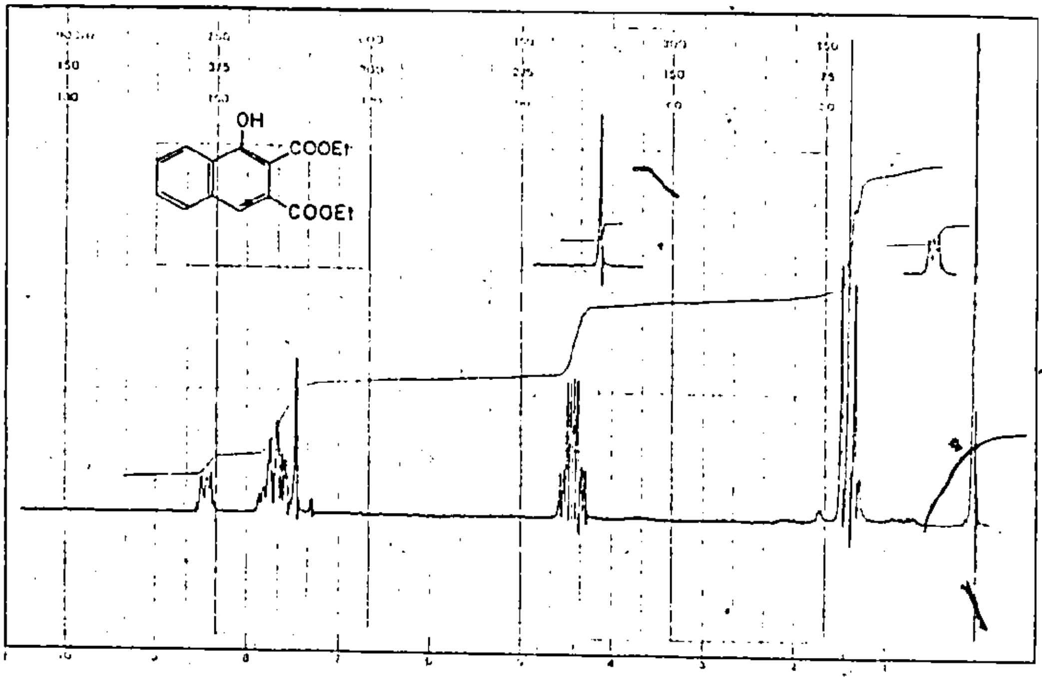


FIGURE 13. ^{1}H NMR spectrum of naphthalene 180.

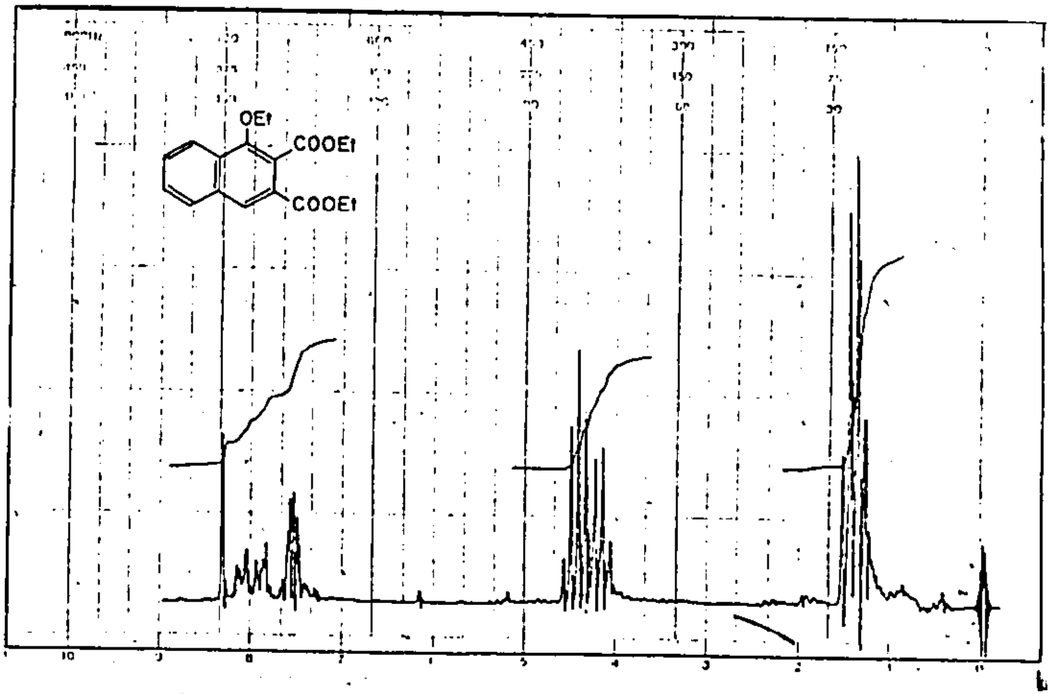


FIGURE 14. ^{1}H NMR spectrum of naphthalene 179.

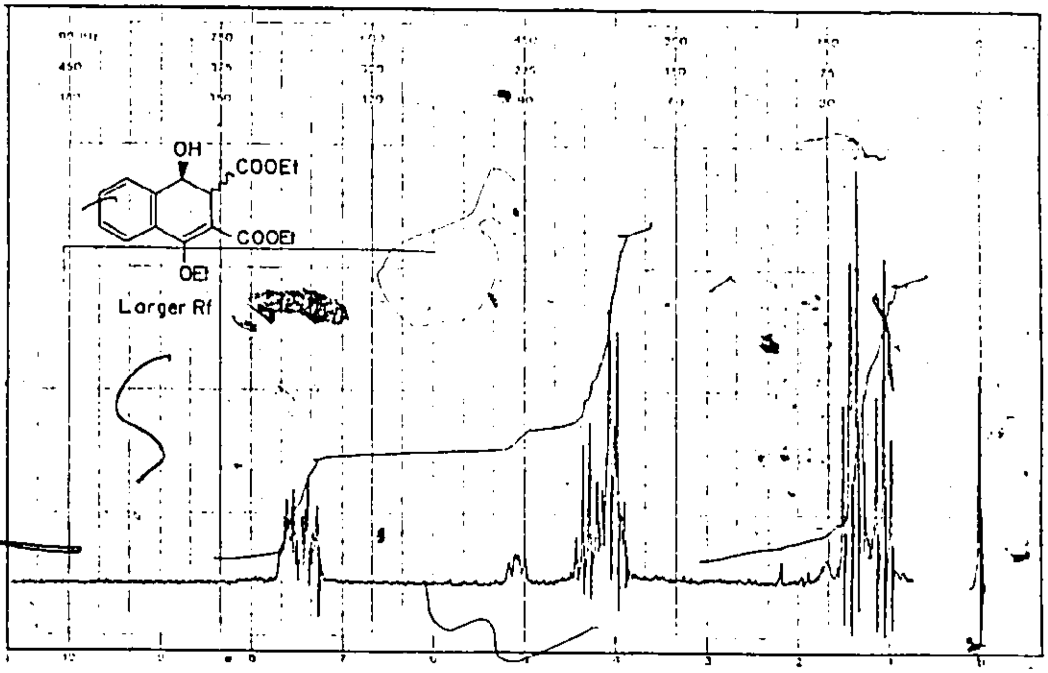


FIGURE 15. ^{1}H NMR spectrum of enol ether 177a.

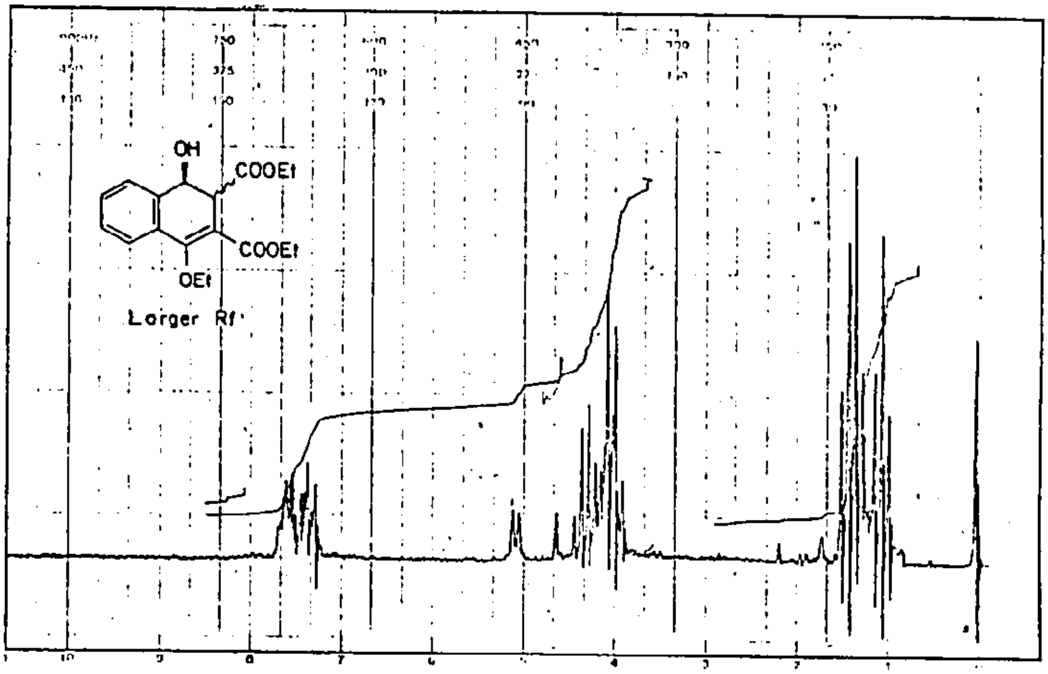


FIGURE 15a. ^{1}H NMR spectrum of enol ether 177a + D_2O.

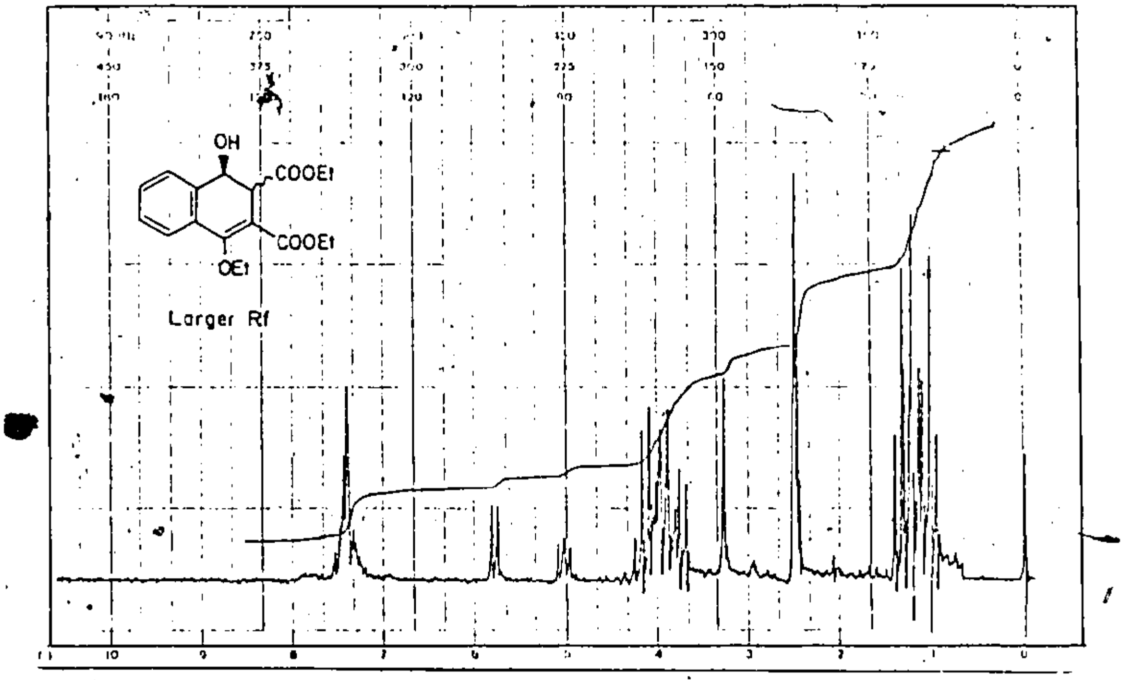


FIGURE 15b. ^{1}H NMR spectrum of enol ether <u>177a</u> in DMSO-d_6.

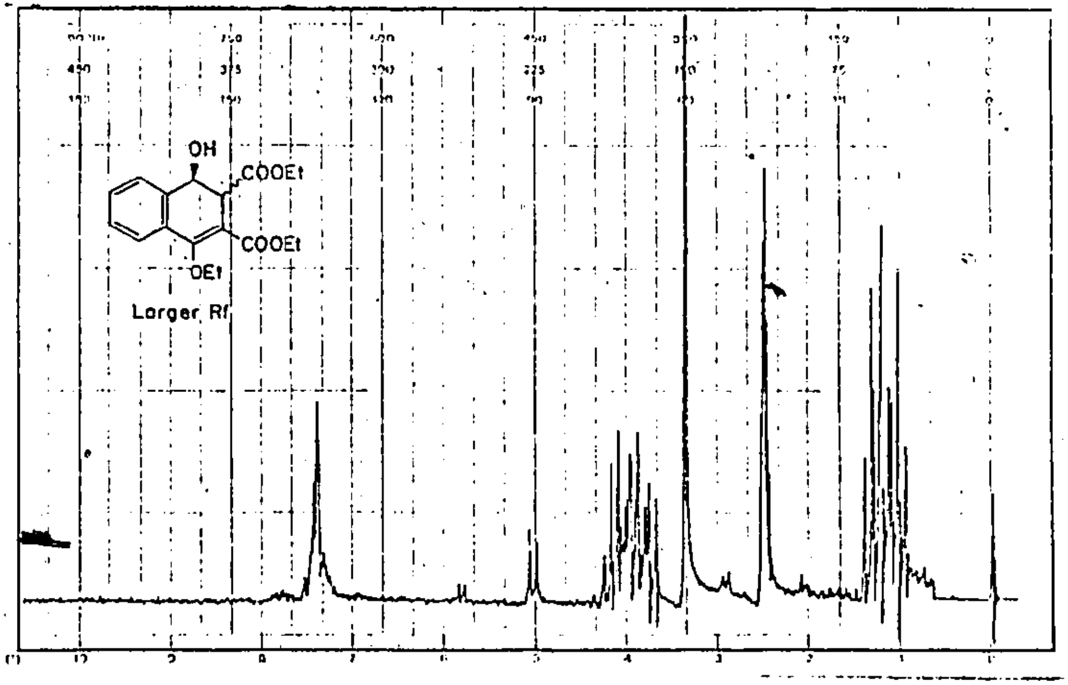


FIGURE 15c. ^{1}H NMR spectrum of enol ether <u>177a</u> in DMSO-d_6 + D_2O.

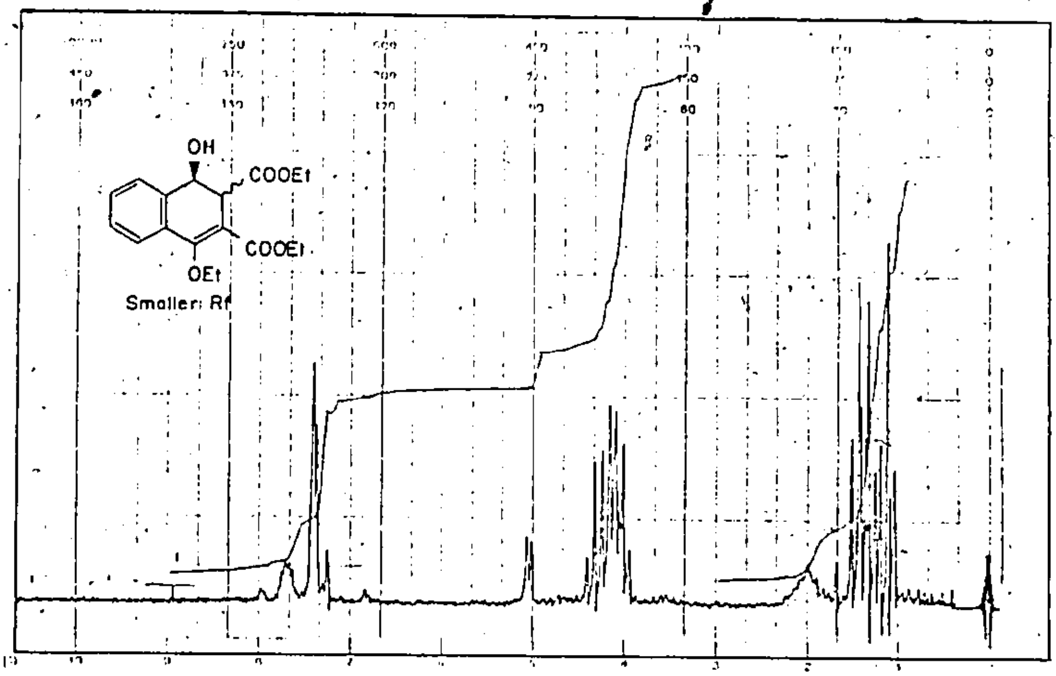


FIGURE 16. ^{1}H NMR spectrum of enol ether 177b.

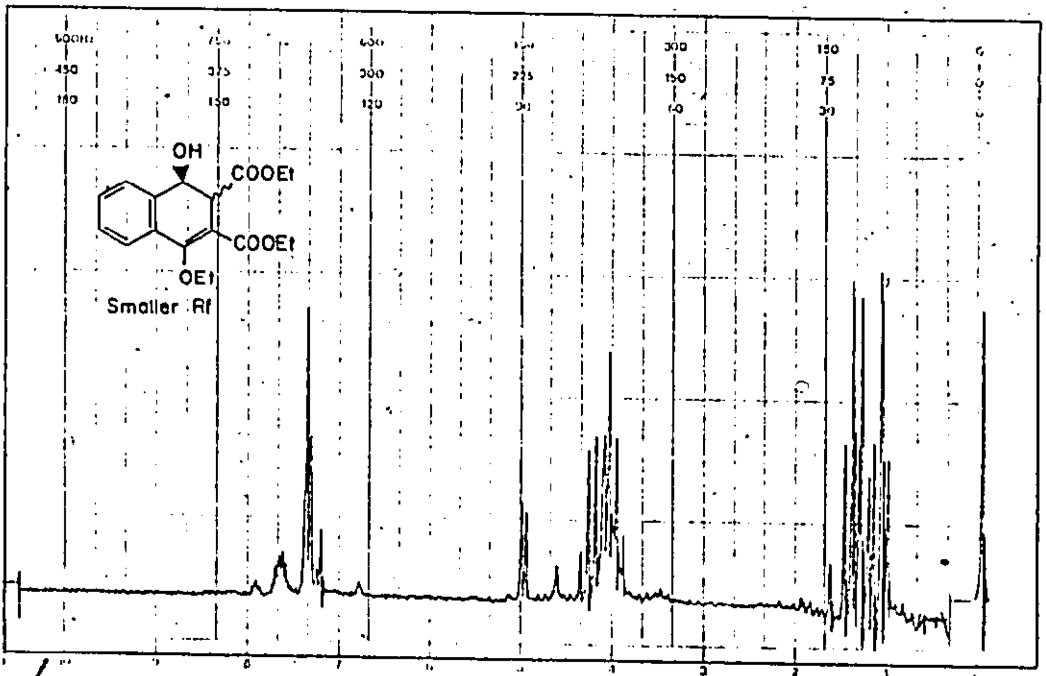


FIGURE 16a. ^{1}H NMR spectrum of enol ether 177b + D_2O.

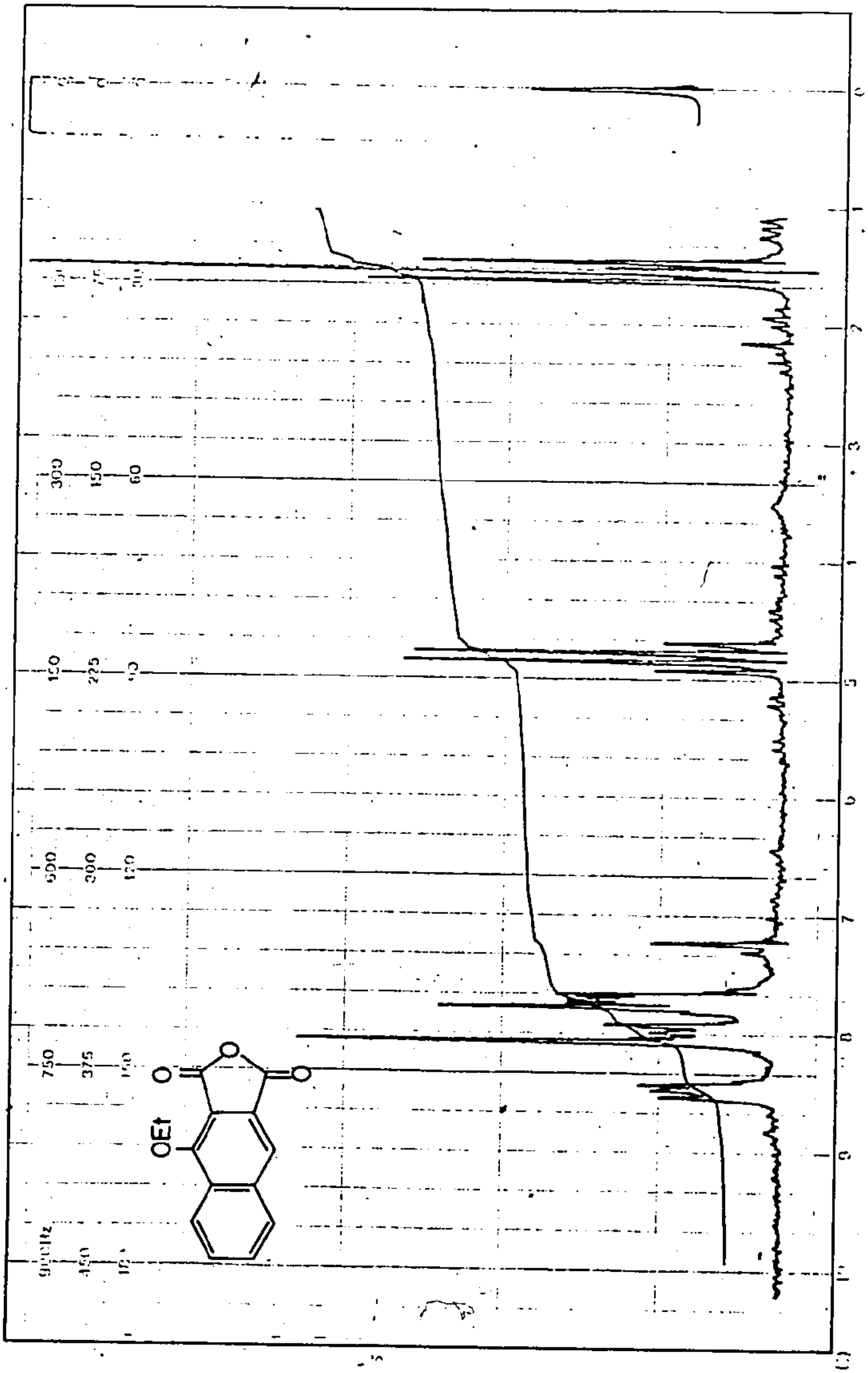


FIGURE 17. ^{1}H NMR spectrum of naphthalene <u>181</u>.

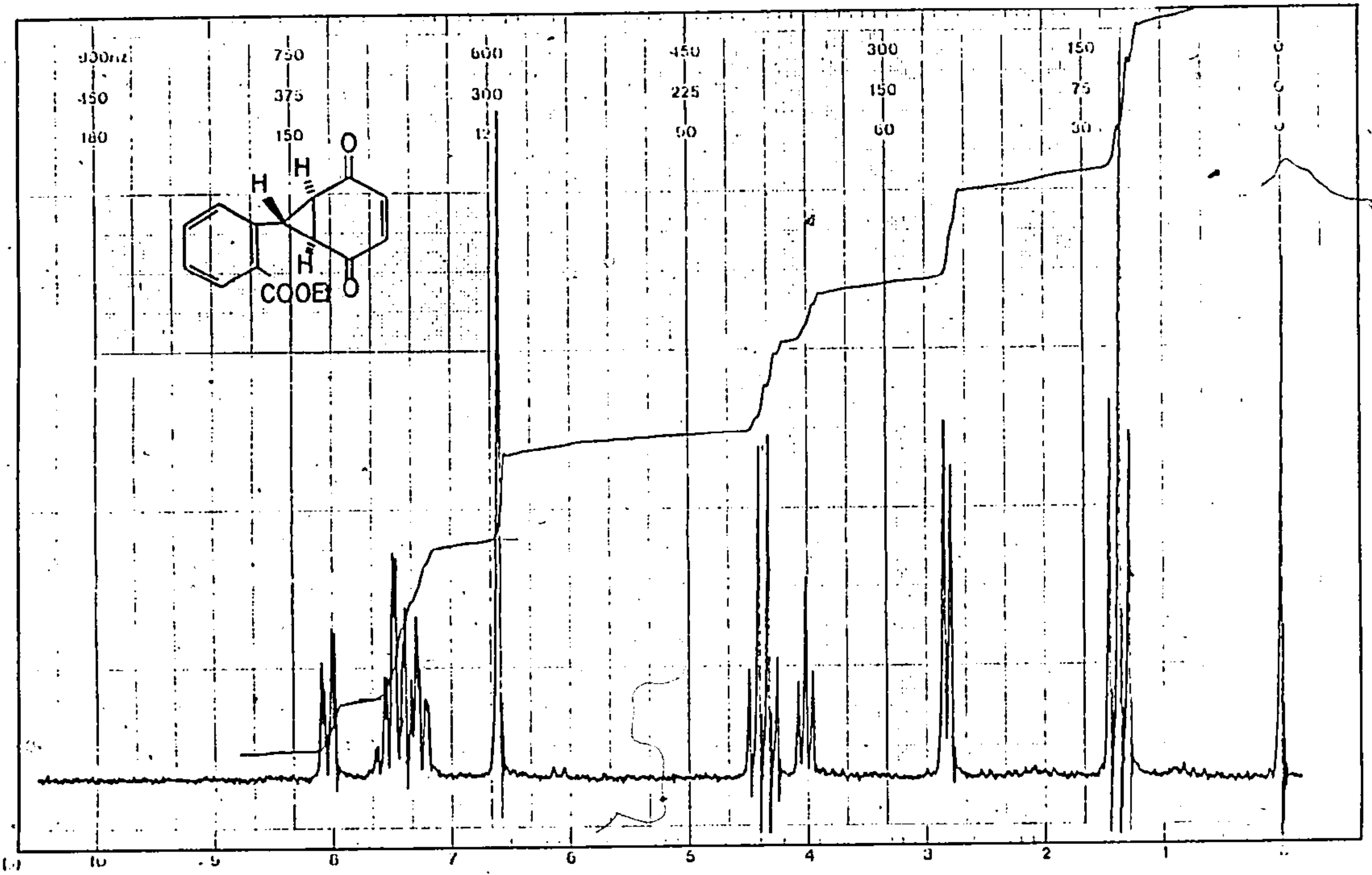


FIGURE 18. ^{1}H NMR spectrum of p-homobenzoquinone 183.

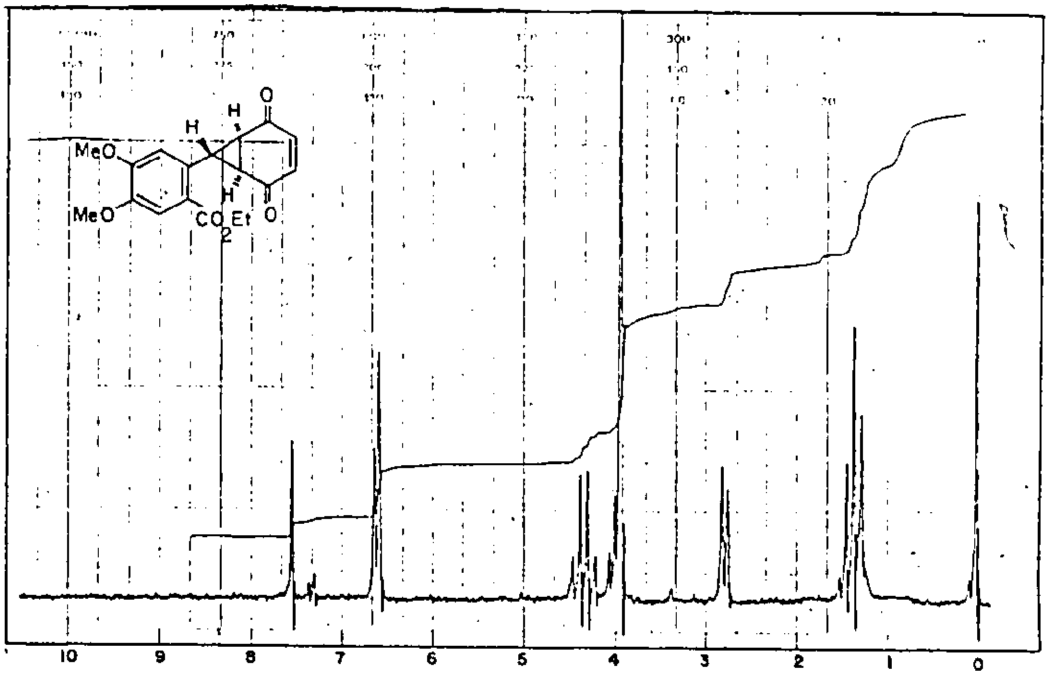


FIGURE 19. ^{1}H NMR spectrum of p-homobenzoquinone 184.

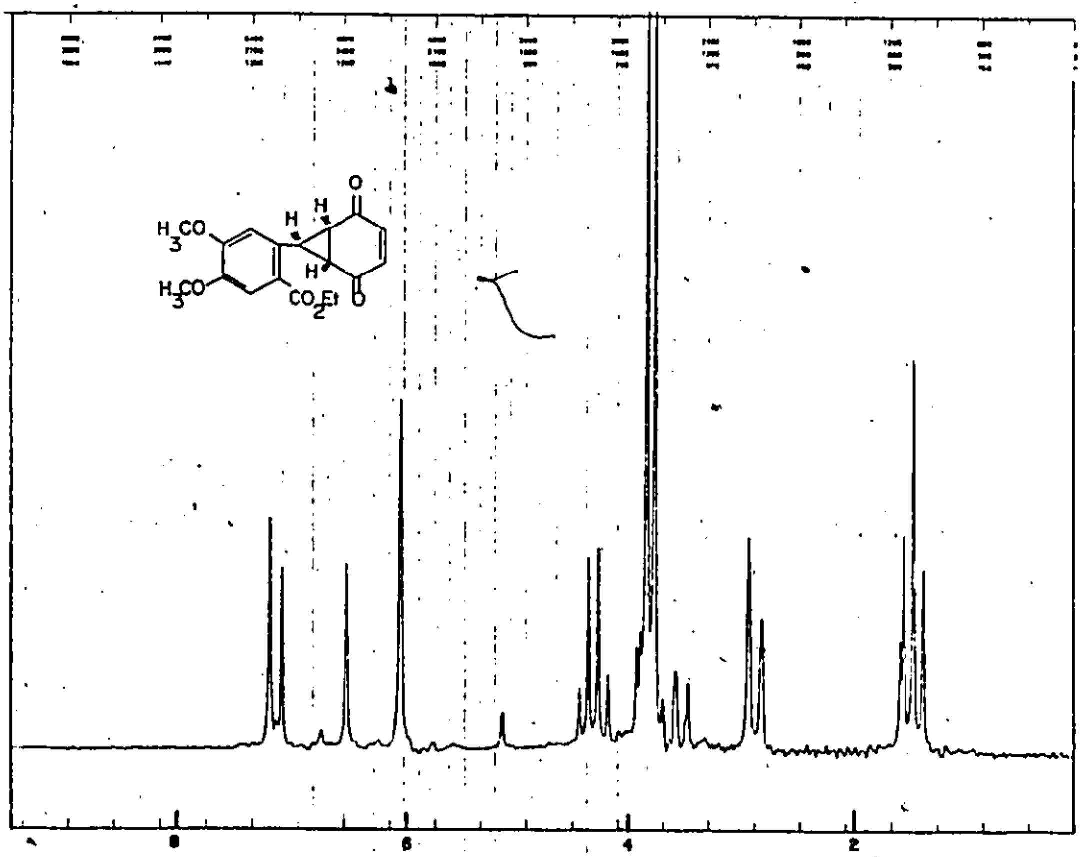


FIGURE 20. ^{1}H NMR spectrum of p-homobenzoquinone 185.

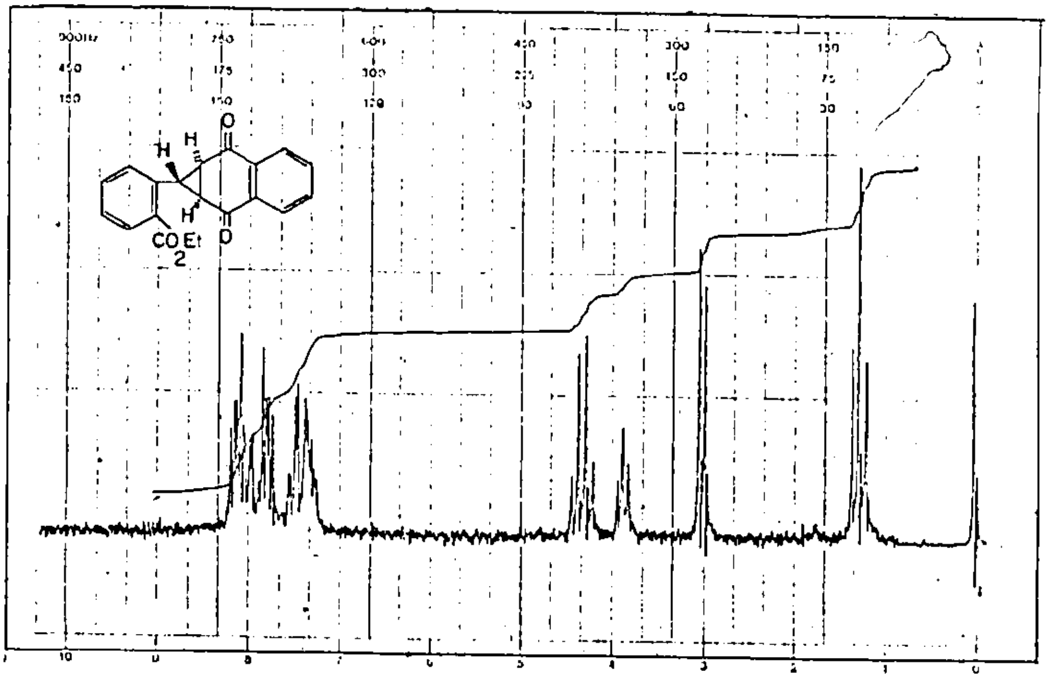


FIGURE 21. ^{1}H NMR spectrum of p-homonaphthoquinone 186.

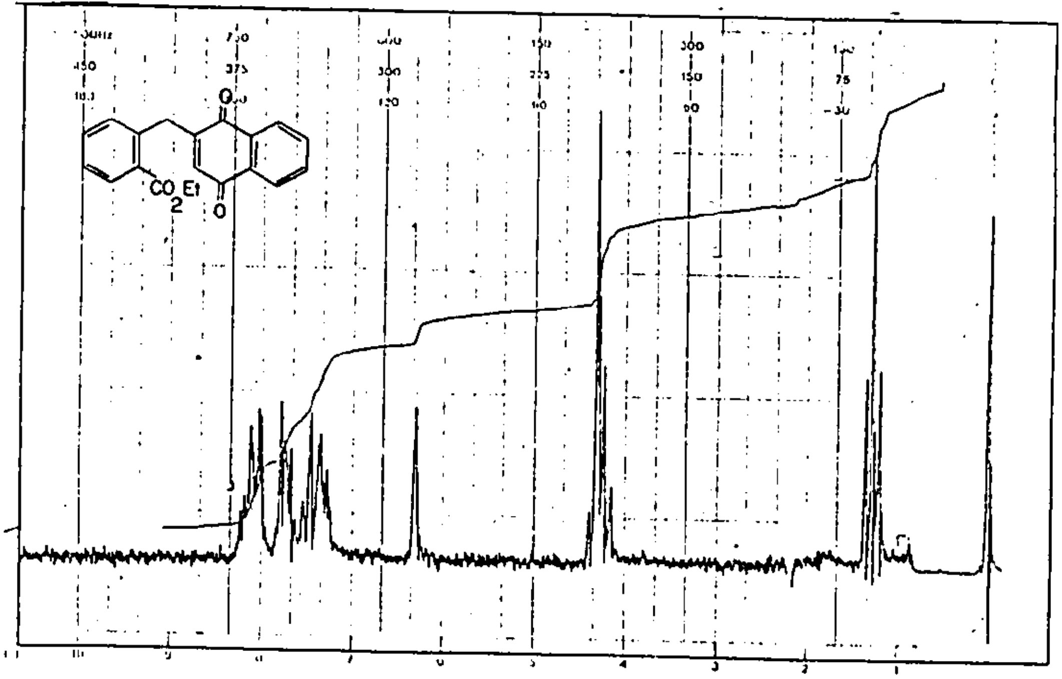


FIGURE 22. ^{1}H NMR spectrum of 187.

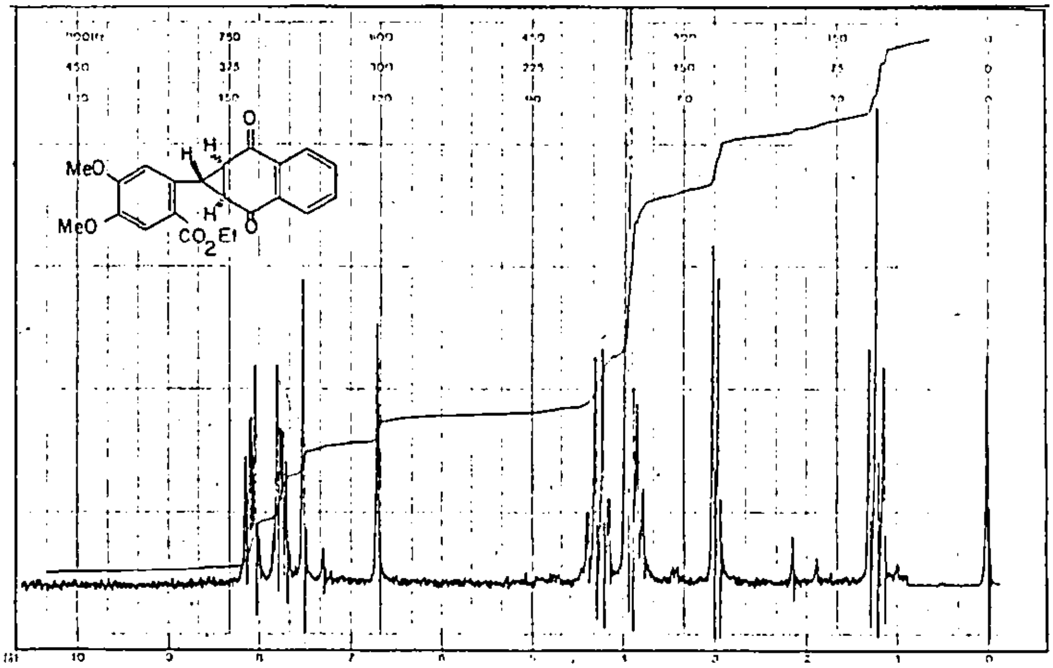


FIGURE 23. ^{1}H NMR spectrum of p-homonaphthoquinone <u>188</u>.

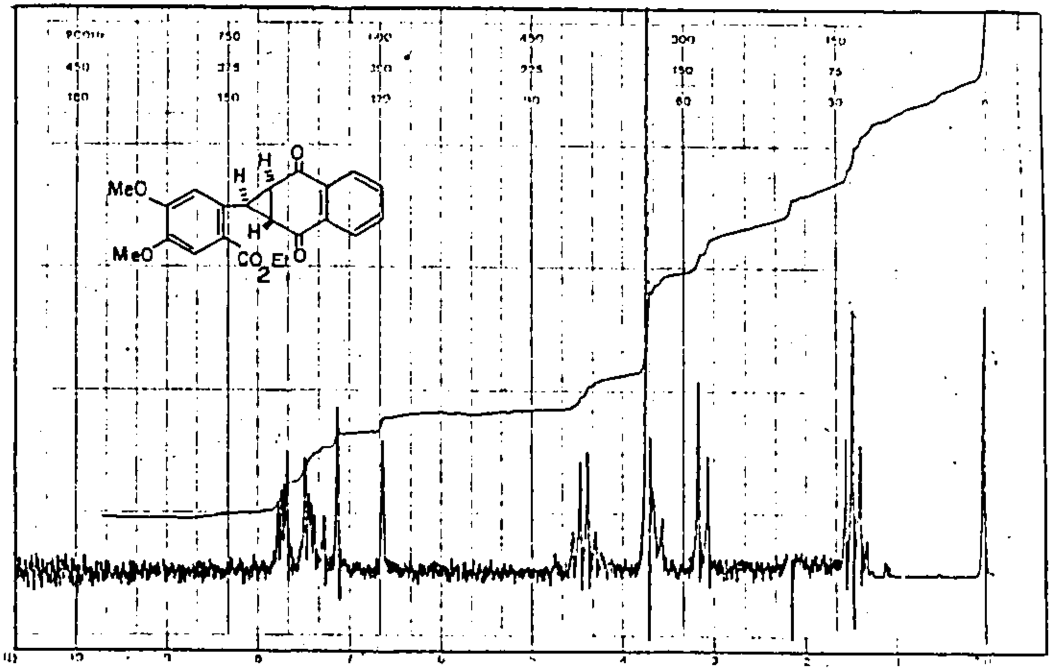


FIGURE 24. ^{1}H NMR spectrum of p-homonaphthoquinone <u>189</u>.

APPENDIX

^{13}C NMR chemical shifts of substituted naphthalenes, tetrasubstituted 1,2-dihydronaphthalenes and compounds 183-187.

TABLE 3. ^{13}C NMR chemical shifts of tetrasubstituted naphthalenes derived from dimethyl acetylenedicarboxylate.

Carbon	139a	139b	140a	140b
1	158.5	157.0	150.9	151.5
2	102.0	100.9	121.4	120.1
3	122.5	121.1	121.4	120.1
4	145.1	144.1	150.9	151.5
5	122.5	101.6	123.6	102.3
6	127.2	150.3	128.3	149.7
7	130.2	152.9	123.6	149.7
8	124.7	103.5	130.5	102.3
9	126.3	127.8	130.5	126.3
10	131.7	127.8	130.5	126.3
1-O$\underline{CH_2}$CH$_3$			72.5	72.0
1-OCH$_2$$\underline{CH_3}$			15.7	15.9
2-$\underline{C}$OOCH$_3$	170.2	170.3	166.9	167.1
2-COO$\underline{CH_3}$	52.5[a]	52.6[a]	52.6	52.5
3-$\underline{C}$OOCH$_3$	168.2	168.4	166.9	167.1
3-COO$\underline{CH_3}$	52.8[a]	52.4[a]	52.6	52.5
4-O$\underline{CH_2}$CH$_3$	72.1	71.7	72.5	72.0
4-OCH$_2$$\underline{CH_3}$	15.7	15.8	15.7	15.9
6-O$\underline{Me}$		55.9		56.0
7-O$\underline{Me}$		56.1		56.0

[a] These assignments may be reversed.

TABLE 4. ^{13}C NMR chemical shifts of naphthalenes 141-145.

Carbon	141	142	143[a]	144	145
1	128.0	151.3	160.5	129.2	130.2
2	125.9	108.9	106.2	130.0	128.6
3	125.9	125.9	125.9	130.0	128.6
4	128.0	120.9	118.4	129.2	130.2
5	128.0	127.8	127.7	128.5	128.6
6	125.9	126.5	129.4	128.5	128.6
7	125.9	125.4	123.3	128.5	128.6
8	128.0	121.6	125.0	128.5	128.6
9	133.6	124.5	124.3	132.9	133.4
10	133.6	134.9	136.9	132.9	133.4
2-<u>C</u>OOH			173.2	168.9	
3-<u>C</u>OOH				168.9	
2-<u>C</u>OOMe					168.2
2-COO<u>Me</u>					52.6
3-<u>C</u>OOMe					168.2
3-COO<u>Me</u>					52.6

[a] $(CD_3)_2SO$

TABLE 6. ^{13}C NMR chemical shifts of substituted naphthalenes derived from unsymmetrically substituted acetylenes.

Carbon	166	167	169	170	172	173
1	150.8	155.7	146.2	158.8	146.2	157.9
2	108.5	104.7	125.9	106.5	124.9	106.3
3	119.3	191.9	113.8	124.4	118.6	129.8
4	148.1	147.1	145.3	145.4	144.7	145.4
5	122.4	122.1	121.6	121.8	122.8	122.4
6	127.0	126.4	126.7	129.5	129.5	127.0
7	127.7	128.9	125.9	125.2	130.4	129.8
8	123.9	123.9	122.5	124.4	123.0	123.9
9	128.4	125.8	125.9	125.2	125.7	125.6
10	130.0	130.3	127.1	131.6	130.4	131.9
2-$\underline{C}OOCH_2CH_3$		171.1		172.6		171.8
2-$COO\underline{CH_2}CH_3$		61.1		61.6		61.0
2-$COOCH_2\underline{CH_3}$		14.3		14.2		13.0
3-$\underline{C}OOCH_2CH_3$	167.3		168.6		167.4	
3-$COO\underline{CH_2}CH_3$	61.6		61.5		61.1	
3-$COOCH_2\underline{CH_3}$	14.3		14.3		13.7	
2-$\underline{CH_3}$			12.7			
3-$\underline{CH_3}$				29.7		
4-$O\underline{CH_2}CH_3$	72.0	64.9	71.9	69.5	72.1	69.6
4-$OCH_2\underline{CH_3}$	15.7	14.9	15.7	15.6	15.8	15.4
2-C_6H_5					128.6,127.0 129.5	
3-C_6H_5						139.2,129.8 127.4,126.2

TABLE 7. ^{13}C NMR chemical shifts of naphthalenes and dihydronaphthalenes derived from diethyl maleate and maleic anhydride by reaction with 127a.

Carbon	177a	177b	178	180	181
1	69.4	68.9	153.4	161.2	157.5
2	46.0	50.2	124.5	103.3	109.3
3	111.6	110.0	130.2	130.8	137.3
4	160.3	159.6	127.6	119.5	121.8
5	124.6	127.8	129.6	127.3	130.0
6	127.8	129.1	127.9	130.2	130.3
7	130.9	130.6	128.7	128.1	131.2
8	124.8	125.0	122.8	124.2	125.6
9	140.8	137.4	126.0	125.5	127.2
10	129.8	130.6	133.9	135.3	131.6
1-OCH$_2$CH$_3$			72.3		72.9
1-OCH$_2$CH$_3$			15.7		16.0
2-$\underline{\text{CO}}$OCH$_2$CH$_3$	172.6	170.9	165.6	170.2	
2-COO$\underline{\text{CH}_2}$CH$_3$	61.3	61.2	61.6	62.1	
2-COOCH$_2$$\underline{\text{CH}_3}$	14.4	14.2	14.2	14.3	
3-$\underline{\text{CO}}$OCH$_2$CH$_3$	166.0	166.3	167.9	169.2	
3-COO$\underline{\text{CH}_2}$CH$_3$	60.8	60.7	61.6	61.5	
3-COOCH$_2$$\underline{\text{CH}_3}$	13.9	14.0	14.2	14.0	
4-O$\underline{\text{CH}_2}$CH$_3$	70.0	70.2			
4-OCH$_2$$\underline{\text{CH}_3}$	15.5	15.5			
2-$\underline{\text{CO}}$					161.5
3-$\underline{\text{CO}}$					163.5

TABLE 10. ^{13}C NMR chemical shifts of the compounds 183-189 derived from reaction of 1,4-benzoquinone and 1,4-naphthoquinone with ortho esters.

Carbon	183	184	186	187	188	189
1	131.5	123.2	131.4	185.0	123.4	
2	137.3	131.3	137.2			
3	127.0	109.8	127.2	126.1	114.6	114.5
4	132.5	152.3	132.5	185.2	152.3	150.8
5	131.5	148.3	131.4	133.7	148.3	150.8
6	128.0	114.3	127.9	132.5	110.0	113.5
7				134.9		
8				133.7		
9				134.3		
10						
11				34.3		
1'	35.8	36.0	36.0	138.5	36.4	34.4
1'a			36.4		36.7	34.0
2'	193.2	193.5	192.2	130.3	192.3	193.0
3'	137.9	137.9	127.2	126.8	177.0	126.0
4'	137.9	193.5	134.3	127.4	134.2	133.7
5'	193.2	36.0	134.3	132.5	134.2	133.7
6'	35.8	36.8	127.2	131.5	127.2	126.0
7'	36.3		192.2		192.3	193.0
7'a			36.4		36.7	34.0
8'			132.8		132.9	134.4
9'			132.8		132.9	134.0
$\underline{C}OOCH_2CH_3$	166.6	166.2	166.8	166.8	166.3	
$COO\underline{CH_2}CH_3$	61.5	61.4	61.5	61.0	61.3	61.6
$COOCH_2\underline{CH_3}$	14.8	14.3	14.1	14.2	14.3	14.3
4-OMe		56.2			56.2	56.0
5-OMe		56.2			56.2	56.0

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