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Preparation of Anthrone and its C-10 derivatives : a literature review

William Paul Blohm
San Jose State University

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**PREPARATION OF ANTHRONE AND ITS C-10 DERIVATIVES:
A LITERATURE REVIEW**

**A Thesis
Presented To
The Faculty of the Department of Chemistry
San Jose State University**

**In Partial Fulfillment
of the Requirement for the Degree
Master Of Arts**

**by
William Paul Blohm
December 1997**

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APPROVED FOR THE CHEMISTRY DEPARTMENT

Dr. Stephen E. Branz
Professor of Chemistry

11/6/97
Date

Dr. Joseph J. Pesek
Professor of Chemistry

11/6/97
Date

Dr. Brenda Kesler
Associate Professor of Chemistry

11/6/97
Date

APPROVED FOR THE UNIVERSITY

Serena M. Stanford

11/21/97
Date

ABSTRACT

PREPARATION OF ANTHRONE AND ITS C-10 DERIVATIVES: A LITERATURE REVIEW

by William Paul Blohm

This thesis provides an inclusive literature review of the titled compounds from 1876 to 1997. Two previous surveys regarding this subject were published in Elsevier's¹ (1939) and Rodd's Chemistry of Carbon Compounds² (1979). The former was a concise summary of the early published synthetic literature while the latter serves as an updated supplement to the former source. Since the last complete review of this subject in 1979, many novel preparations have been developed thus permitting further access to both C-10 mono- and disubstituted anthrone derivatives. Recent work has permitted access to previously inaccessible, sterically congested anthrone derivatives. In addition, significant data has been accumulated concerning some unusual solid and solution state conformations of anthrone and its C-10 derivatives. Additional topics of this review include improved synthetic preparations and the preparation of spirocyclic ring systems.

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Introduction

The chemistry of anthrone and anthraquinone have played and will continue to play an important part of modern organic chemistry. These compounds and their derivatives have numerous applications that include: dye synthesis,³ pharmaceutical drug development,^{4,5} delignification of wood pulp,^{6,7} kinetic studies of keto/enol tautomerization,⁸⁻¹⁰ as well as mechanistic¹¹ and conformational investigations¹¹ of sterically congested polycyclic molecules.

The first synthesis of anthrone was performed by Liebermann¹³ in 1876 through the four-electron partial reduction of anthraquinone (Scheme 1). Anthraquinone (1) and anthrone (2) are tricyclic compounds derived from anthracene (Scheme 2). The syntheses of anthraquinone and anthrone ultimately led to the preparation of synthetic dyes which in turn led to a greater understanding of the structure, reactivity, and ultimately the mechanistic pathways.

The IUPAC name for anthrone is 9,10-dihydro-9-anthracenone. For the sake of simplicity, this thesis will use the classical and still commonly employed term, anthrone. The compounds depicted in Scheme 3 differ in oxidation state with regards to the central ring of anthrone. Through chemical

manipulation of the oxidation state of anthrone's C-9 and C-10 carbons (Scheme 3), a wide variety of synthetic products and potential starting materials are synthetically feasible. The term "oxidation" and "reduction," within this thesis, will refer only to the central ring of anthrone or any other polycyclic anthracene derivative unless specifically noted otherwise.

The apparent simplicity of anthrones and the novelty of their preparations make this class of compounds interesting synthetic targets. A considerable amount of effort has been devoted towards the synthetic preparation of anthrone and its C-10 mono- and disubstituted derivatives. For example, one of the primary complications of the early synthetic efforts to prepare 10,10-dialkylated anthrones was the formation of multiple products during alkylation reactions of anthrone. Undesired side products included anthronyl (previously known as anthryl) ethers (Scheme 4).

This thesis will review the preparation of anthrone and derivatives substituted at the C-10 position through redox neutral reactions (as defined later within this thesis) and manipulation of the oxidation state of the C-9 and C-10 carbons of anthrone's central ring system. Additionally, keto/enol tautomerization, solution and solid state conformations, and change in the oxidation state for C-9 and C-10 carbons of the substrate will also be

addressed. These syntheses are classified in their respective sections according to the synthetic strategies, modes of bond formation, and product(s) formed. These strategies are grouped under common headings that permit comparison of alternative methods of preparation by the same or closely related methodologies.

The most recent comprehensive review of anthrone synthesis and C-10 mono- and disubstituted anthrone derivatives was published in Rodd's Chemistry of Carbon Compounds² (1979). Since that publication, significant improvements in preparation of C-10 mono- and dialkyl/aryl and C-10 heteroatom anthrone derivatives have been published. This thesis will focus on these recent advances as well as the classical syntheses of anthrone and its C-10 derivatives. Some classical syntheses from the nineteenth century have yet to be supplanted by more modern methodologies.

One additional purpose of this thesis is to explore the concept of oxidation and reduction of a substrate to yield anthrone and the C-10 substituted derivatives. To exemplify on this concept of oxidation, the preparation of 10,10-dimethylantrone from 9,10-dihydroanthracene is defined as a 4-electron oxidation reaction. Within the context of this thesis, the oxidation and reduction of substrates for the preparation of anthrone and its C-10

substituted derivatives will be defined as the change in the functional group family (ΔFGF) of the central ring with the formal oxidation state of both the carbon-hydrogen and carbon-carbon is defined as identical (a value of zero). Therefore, as an example, 10,10-dimethylanthrone and anthrone exist at oxidation states of zero (Scheme 3, Class C) and 10,10-dimethoxyanthrone, 10,10-dibromoanthrone and anthraquinone all exist at the +4 oxidation state (Scheme 3, Class A). Scheme 3 depicts a series of anthracene derivatives that are classified by oxidation state; Class C, as well as the other 4 classes, readily undergo functional group interconversion reactions to yield product without a change of the formal oxidation state. Functional class interconversion reactions for any of the 5 classes of reactions in Scheme 3 may be considered a feasible strategy given the proper reaction conditions and reagents. Some of the physical properties of anthrone are listed in Scheme 5.

Scheme 1: Classical Synthesis of Anthrone Via a Four Electron Partial Reduction of Anthraquinone¹⁴

Scheme 2: Functional Class Interconversion Reaction of Anthracene Derivatives

Scheme 3: Oxidation State of Related Polycyclic Molecules

A

Functional Class:
(Z - (H, C))

+4

X = Halogen or OMe

B

+2

R = H, Alkyl or Aryl
Y = OH, Halogen or NO₂

C

0

R = H, Alkyl or Aryl

D

-2

R = H, Alkyl or Aryl

E

-4

R = H, Alkyl or Aryl

Scheme 4: Multiple Product Formation During 10,10-Dimethylanthrone Synthesis

Scheme 5: Properties of Anthrone

Common Name: Anthrone

IUPAC Name: 9,10-Dihydro-9-Anthracenone

Formula: $C_{14}H_{10}O$

MW = 194.232

Percent Composition: C (86.57%), O (8.24%), H (5.19%)

Significant features of Anthrone:

- Peri hydrogens at positions denoted by *
- Benzhydrylic hydrogens at the C-10 position
- Acidity of the C-10 methylene group greatly increased by resonance stabilization of the conjugate base, the vinylogous enolate. Result: a methylene group that is readily deprotonated by hydroxide or methoxide.
- A planar structure for the tricyclic ring system.

Synthesis of Anthrone

The synthesis of anthrone has been accomplished by a wide variety of methodologies which can be described by one of the five following classifications: (1) the reduction of anthraquinone, (2) Bronsted acid induced cyclization reactions, (3) Lewis acid catalyzed, Friedel-Crafts cycloaddition reactions, (4) oxidation of anthracene and C-9 substituted anthracenes, and (5) Diels-Alder reactions with benzyne. The first four methodologies were extensively investigated and developed by the end of the 1939. The classic example of anthrone synthesis, still widely employed today, was developed by Meyer^{14,15} in 1911. This procedure is a 4-electron partial reduction of anthraquinone¹⁴ (Scheme 6). The proposed mechanism involves a 10-hydroxyanthrone intermediate (not shown in Scheme 6). The advantages of this particular synthesis included the ease of the process, minimal side product formation, final purification by recrystallization, and the lack of need for an inert gas atmosphere.

Scheme 6: Reduction of Anthraquinone to Yield Anthrone¹⁴

Examples of Bronsted acid catalyzed cyclodehydration reactions would include Fieser and Hershberg's application of hydrofluoric acid¹⁶ or Fisher and Schmidt's use of sulfuric acid.¹⁷ Combination of either acid with ortho-benzylbenzoic acid (3) result in anthrone formation (Scheme 7). Formation of a strong electrophile by protonation of the carboxylic acid in solution, followed by electrophilic attack by the phenyl ring, loss of a phenyl proton, and rearomatization of the ring system generates the desired product, 2.

The Lewis acid catalyst, aluminum(III) chloride, has been the sole catalyst used to form anthrone from phthalide or phthalic anhydride (with a later reduction step) in a benzene solvent system¹⁸ (Scheme 8) or ortho-bromo-methyl benzyl bromide.¹⁹ The phthalide (4) reaction has a relatively poor yield of 28%. Addition of the appropriate Lewis or Bronsted acid catalyst, with their respective substrates described above, also catalyze the formation of strong electrophiles by coordination of the acid (Lewis or Bronsted) with the carbonyl. These electrophiles in turn undergo inter- or intramolecular nucleophilic attack by an aromatic ring system. This general approach has been used to prepare an exceptionally large number of anthrone derivatives substituted with electron donating groups at carbons C-1 (or C-3). The description of these derivatives is beyond the purpose and scope of this thesis and therefore has not been included.

Scheme 7: General Conditions for Cyclodehydration To Form Anthrone^{16,17}

Scheme 8: Friedel-Crafts Reaction To Form Anthrone¹⁸

The remaining two synthetic procedures to prepare anthrone were developed primarily from research into large polycyclic ring formation reactions. The first synthesis was described by Whitlock²⁰ (Scheme 9) as an “equivalent to the Friedel-Crafts cycloacylation reaction” leading to anthrone. The addition of excess *n*-butyl lithium to a solution of ortho-(ortho-bromobenzyl)benzoic acid, **5**, simultaneously deprotonates and debrominates the substrate. The phenyl anion then nucleophilically adds to the carbonyl of the carboxylic anion resulting in formation of the dilithium salt of the gem-diol, **6**. Upon acidification anthrone, **2**, is formed in 74% yield. The overall reaction is a two-electron reduction for each step of Scheme 9.

The final preparation of anthrone to be reviewed was developed by Rickborn et al.²¹ (Scheme 10). Acetal (**7**) is converted to the 1,3-bis(trimethylsilyl)isobenzofuran, **8**. The in situ generation of a highly reactive benzyne intermediate, **9**, upon addition to isobenzofuran, **8**, forms the bis(trimethylsilyl)-ether, **10**, by way of a Diels-Alder reaction. In the final step, **10** was combined with trifluoroacetic acid to yield anthrone, **2**. The benzyne intermediate may also contain C-3 to C-6 halogen, methyl, methoxy, polycyclic functional groups (or a combination of these groups) that permit synthesis of substituted or extended polycyclic ring derivatives of anthrone (Scheme 10).

Scheme 9: Anionic Equivalent to the Friedel-Crafts Cycloacylation Reaction²⁰

Proposed Intermediate:

Scheme 10: Synthesis of Anthrone from Isobenzofuran and Benzyne²¹

A summary of the synthetic methodologies to prepare anthrone is compiled in Table 1. The tables that follow throughout this thesis include the following data: substrate employed, summary of reaction conditions used to form the product, product formed, percent yield, ΔFGF , reference, and spectra recorded. (ΔFGF is defined as the overall change oxidation state of the substrate versus the product). The “-” and “+” symbols indicate reduction and oxidation (respectively), and the number of electrons involved, while “0” indicates a redox neutral reaction. Of particular note, the spectral sections only specify the application of infrared (IR), ultraviolet (UV), mass spectral (MS), and nuclear magnetic resonance (NMR) analysis. NMR refers to the proton NMR only, unless otherwise noted as ^{13}C -NMR. Elemental analysis was universally performed in all papers reviewed, therefore it is not noted.

In addition, numerous errors in structural assignments of anthrone and related compounds have resulted from assignments based solely on elemental analysis. In cases where spectral analyses were performed but not included in the paper, the information was tabulated as NR (not recorded), otherwise it was tabulated as NA (not available). Even within the past 30 years, a surprising number of papers have been published without supporting spectral data.

Numerous additional preparations of anthrone have been published but have not been recorded in this thesis. These methods are not readily applicable to the synthetic laboratory for the preparation of 1 to 100 gram quantities of anthrone or product yield was low in comparison to the total number of products isolated. Two such syntheses in the former class of reactions included the electrolytic reduction of anthraquinone²² under acidic and high pressure conditions and laser jet photochemical transformation of 2-methyl benzophenone²³ (milligram quantity). An example of the latter class of reactions included the application of benzyl benzoate²⁴ to aluminum oxide catalyst at 350 °C with over 10 products isolated.

Table 1. Preparation of Anthrone

Entries 1 - 17

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
1	Anthraquinone (1)	Sn/HCl/AcOH (reflux)	82.5	-4	13	NA
2	Anthraquinone	Sn/HCl/AcOH (reflux)	82	-4	14, 15	NA
3	Anthraquinone	Al/H ₂ SO ₄	NA	-4	25	NA
4	Anthraquinone	H ₂ /Ni salts Decalin reflux	NA	-4	26	NA
5	Anthraquinone	Triethanol- amine	NA	-4	27	NA
6	Anthraquinone	1) NaBH ₄ /MeOH 2) HCl	60	-4	28	IR/NMR

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
7	Anthracene (2)	HNO ₃ /AcOH Sn/PtCl ₄ /HCl	NA	+2	29	NA
8	9-NO ₂ - Anthracene	Sn/AcOH	NA	0	30	NA
9	1) Anthracene 2) 9-Br- Anthracene 3) 9-MeO- Anthracene	1) CuBr ₂ 2) NaOMe 3) HCl/aq. AcOH	60.8	+2	31	NA
10	<i>o</i> -Benzyl- benzoic acid	H ₂ SO ₄ /90 °C	NA	0	17	NA
11	<i>o</i> -Benzyl- benzoic acid	HF	82	0	16	NA
12	<i>o</i> -Benzyl- benzoic acid	Xylene (reflux) Nafion resin	81	0	32	NA
13	<i>o</i> -Benzyl- benzoyl chloride	Nafion resin/ C ₆ H ₆	71	0	32	NA
14	<i>o</i> -Benzyl- benzoyl bromide	C ₆ H ₆ /AlCl ₃	NA	0	18	NA
15	(1(3H)-iso- benzofuranone)	C ₆ H ₆ /AlCl ₃	28	0	19	NA
16	<i>o</i> -(<i>o</i> -bromo- benzyl) benzoic acid	1) -80 °C/2.5 eq. <i>n</i> -C ₄ H ₉ Li 2) H ₃ O ⁺	74	0	20	NA
17	1,3-bis(tri- methylsilyl) isobenzofuran	1) <i>n</i> -C ₄ H ₉ Li/ BrC ₆ H ₅ 2) TFA	74	0	21	NMR

Halogenation of Anthrone

Anthrone has been the most common substrate for preparation of more complex C-10 anthrone derivatives. In order to employ powerful synthetic methodologies for carbon-carbon bond formation, derivatization of anthrone at the C-10 position is often required. Following the synthesis of anthrone itself, the application of Friedel-Crafts chemistry to anthrone was begun immediately. The preparation of C-10 mono- and dihalogenated anthrone derivatives was mandatory if structural derivatives were to be prepared via Friedel-Crafts conditions. The halogenation of anthrone can result in the formation of the monohalogen (Cl, Br) or dihalogen (F, Cl, Br) derivatives. The oxidation state of these halogenated compounds is +2 and +4, respectively. To date, no synthetic preparations for 10-monofluoro-, 10-monoiodo-, or 10,10-diiodoanthrone have been reported.

Formal oxidation of the substrate has been the sole method to prepare 10-mono- or 10,10-dihalogenated anthrone except for synthetic preparations of 10-monohalogenated anthrone from 10-hydroxyanthrone (entries: 19/20 Table 2). This latter reaction involves functional group interconversion of the hydroxyl group to a halogen by the addition of mineral acid to the solution. Scheme 11 depicts the above reaction, beginning with anthrone deriva-

tive 11. Reagents employed for the conversion of 10-hydroxyanthrone to 10-monohaloanthrone derivatives include chlorine gas and iodine, hydrochloric and hydrobromic acid. Addition of either of these strong mineral acids to solutions of 10-hydroxyanthrone (11) or 9,10-peroxy-9,10-dihydroanthrone³⁷ (12, which generates, 11, in situ) results in protonation of the C-10 hydroxyl group, nucleophilic attack of the halogen anion on C-10 carbon of anthrone, followed by dehydration. The product 13 or 14 is formed.

Scheme 11: Formation of 10-Bromo- and 10-Chloroanthrone³⁷

A classic preparation of both the 10-mono- and 10,10-dibromoanthrone was developed by Goldmann in 1887.³⁴ This method, still commonly cited in journal literature preparations, employs either 1.0 or 2.2 equivalents of bromine in carbon disulfide to yield 10-bromoanthrone³³ (**15**) or 10,10-dibromoanthrone³³ (**16**), respectively (Scheme 12). The desired product was reported to precipitate from solution in high yield.

N-Bromosuccinimide³⁴ and thionyl bromide³⁵ have also recently been demonstrated as effective brominating agents to prepare both **15**³⁴ and **16**.³⁵ The analogous use of thionyl chloride³⁶ in dioxane to prepare 10,10-dichloroanthrone was not as effective as thionyl bromide as a halogenating agent as measured by overall yield and side product formation.^{35,36} In addition, 10,10-difluoroanthrone^{38,39} **17** has also been prepared (Table 4). One successful synthesis of **17** reported by Applequist³⁸ utilized SF₄, HF, and anthrone heated under pressure was (Scheme 13).

Tables 2, 3, and 4 summarize the preparation of 10-mono- and 10,10-dichloroanthrone, 10-mono- and 10,10-dibromoanthrone, and 10,10-difluoroanthrone, respectively. The formation of these mono- and dihalogenated derivatives of anthrone yields products at the +2 and +4 oxidation states, respectively. These mono- and dihalogenated anthrone derivatives have

most commonly been used in Friedel-Crafts reactions to prepare C-10 aryl derivatives of anthrone to be reviewed later in this thesis.

Scheme 12: Preparation of 10-Bromoanthrone Derivatives³³

Scheme 13: Formation of 10,10-Difluoroanthrone³⁷

Two additional examples of 10,10-dihalogenated anthrone applications have been in the preparation of 10-dicyanomethyleneanthrone⁴⁰ and 10-diazoanthrone;⁴¹ the latter product is an extremely useful substrate for 10-spirocycloanthrone preparation. The following list summarizes the substrates employed to date for the preparation of C10-halogenated anthrones: anthrone, anthracene, anthranyl acetate (or derivatives), 9,10-peroxy-9,10-dihydroanthracene, or ortho-methylbenzophenone.

Table 2. Preparation of 10-Chloroanthrone (Entries 18 - 23) and 10,10-Dichloroanthrone (Entries 24 - 27)

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
<u>10-Chloroanthrone</u>						
18	Anthrone	Cl ₂ /CCl ₄ I ₂ (trace)	NA	+2	53	NA
19	10-Hydroxy-anthrone	HCl/reflux	NA	0	54	NA
20	10-Hydroxy-anthrone	HCl (gas)/ Toluene	NA	0	55	NA
21	Anthranyl acetate	Cl ₂ /AcOH	NA	+2	56	NA
22	9,10-peroxy-anthracene	HCl	NA	+2	57	NA
23	Anthrone	SOCl ₂ /Dioxane	41	+2	58	NA

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
<u>10,10-Dichloroanthrone</u>						
24	Anthrone	Cl ₂ /CHCl ₃	NA	+4	59	NA
25	<i>o</i> -(methyl benzo)-phenone	Cl ₂ /110-20 °C	NA	+4	60	NA
26	<i>o</i> -(methyl benzo)-phenone	Cl ₂ /180 °C	NA	+4	61	NA
27	Anthrone	SOCl ₂	NA	+4	62	NA

Table 3. Preparation of 10-Bromoanthrone (Entries 27 - 33) and 10,10-Dibromoanthrone (Entries 34, 35)

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
<u>10-Bromoanthrone</u>						
28	Anthrone	Br ₂ /CS ₂	85	+2	63,64	NA
29	Anthronyl acetate	Br ₂ /AcOH	NA	+2	65	NA
30	Anthronyl-phenyl acetate	Br ₂ /AcOH	NA	+2	66	NA
31	Anthracene	Br ₂ /Dioxane	33	+4	67	NA
32	Anthrone	NBS/C ₆ H ₆ / <i>hν</i>	91	+2	68	NMR/IR/MS
33	9,10-peroxy-anthracene	HBr	NA	+2	69	NA

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
<u>10,10-Dibromoanthrone</u>						
34	Anthrone	Br ₂ /CS ₂	85	+4	70	NA
35	Anthrone	SOBr ₂ /C ₆ H ₆	NA	+4	71	NA

Table 4. Preparation of 10,10-Difluoroanthrone (Entries 36, 37)

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
36	Anthrone	SF ₄ /HF/69 °C CH ₂ Cl ₂ /heat	85	+4	72	NA
37	Anthraqui- none	SF ₄ /HF	10	0	73	NMR/IR

Formation of C-10 Mono- and Disubstituted Derivatives of Anthrone

The formation of the C-10 mono- or 10,10-dialkyl/aryl substituted anthrones is the primary focus of this thesis. Anthrone itself has only seventeen preparations that can be partitioned into 5 classes of reactions. In comparison, there are over four hundred fifty reported preparations of C-10 anthrone derivatives. Many of these preparations can be described in terms of classical base promoted carbonyl chemistry. The simplest example is the hydroxide deprotonation of anthrone to yield the conjugate enolate that is then treated with an alkylating reagent. These earliest experiments suggested dialkylation reactions involving anthrone would require significantly greater knowledge and understanding of organic chemistry and reaction mechanisms to increase the yield and specificity of the alkylation process. As a second example, Friedel-Crafts arylation reactions have been used to prepare C-10 mono- or diarylanthrones. While this reaction is efficient, it is also limited in its utility to prepare a large variety of anthrone derivatives. Organic chemists endeavored to design reactions such that any alkylating reagent could be employed to prepare C-10 sterically congested anthrones with non-equivalent substituents. Many of the earliest successful preparations of substituted anthrones had been designed for specific alkylating reagents.

Some of the most notable obstacles encountered during anthrone preparation included: air oxidation, counterion and polar solvent effects with base deprotonation reactions, 9-anthranyl ether side products, and formation of severely sterically hindered 10,10-disubstituted anthrones. In response to the last issue, anthrone was not the substrate utilized; instead, other anthracene derivatives were employed. Each of these obstacles was eventually overcome but required almost 100 years before all the issues were satisfactorily resolved.

Data regarding the formation of anthrone derivatives were organized such that comparison of related reactions are readily accomplished. The formation of C-10 mono- or dialkyl or 10-arylanthrones within this thesis was organized by the following reaction conditions: hydroxide and alkoxide promoted alkylation reactions, acid-catalyzed cyclodehydrations and Friedel-Crafts reactions, oxidation of starting materials with prior alkyl group incorporation, and carbon-carbon double bond formation at the C-10 position of anthrone including bianthrone and bianthrylidene. Additional topics include: Grignard and related metal salt reducing reagents as nucleophiles, formation of C-10 spirocycloanthrones, and formation of C-10 substituted anthrones through thermal, photochemical, radical, and concerted reactions. The final two sections describe keto/enol tautomerization of anthrone and conformational

and spectral analysis of anthrone and C-10 substituted derivatives.

Each of the above reaction classifications will be described in further detail with several examples presented for each of the later sections. The data within each titled section presented typically parallels the historic development of anthrone reaction chemistry with the earliest synthetic work presented at the beginning of a table while the most recent work can be found at the end of the table. Discussions for each section are organized in a similar fashion.

Hydroxide and Alkoxide Promoted C-10 Alkylation of Anthrone

The earliest attempts from the 1880's to the early 1950's to alkylate anthrone employed potassium hydroxide as the base to generate the anion that was then treated with alkyl iodide. This strategy had only limited success as formation of multiple products occurred and only a small percentage of the desired product was formed (Scheme 4,⁵³ Introduction).

9,10-Dihydroanthracene (DHA, **18**) has a pKa of approximately 35. The conjugate base of 9,10-dihydroanthracene (DHA), **19**, is stabilized by its two aryl substituents by both resonance and inductive effects (Scheme 14). In contrast to DHA, the C-10 carbon of anthrone is a significantly stronger carbon acid (pKa of approximately 15) and can be readily deprotonated by hydroxide or methoxide. Anthrone's greater acidity relative to **19** is due to resonance in which the oxygen stabilizes the negative charge, forming **20** (Scheme 15). The properties of **20** can be represented by its two major resonance structures **20A** and **20B**. One common complication with potassium hydroxide deprotonation reactions of anthrone had been the formation of unwanted side products described above. The reported yield of 10,10-dimethylanthrone⁷⁶ from the mixture of potassium hydroxide, methyl iodide, and anthrone under aqueous reflux was reported to range from 0 to 3 %.

Scheme 14: Deprotonation of 9,10-Dihydroanthracene and the Major Resonance Structures of the Resulting Anion

Additional resonance structures not shown for 19 or 20

**Scheme 15:
Deprotonation of Anthrone and the
Major Resonance Structures of the
Resulting Enolate Anion**

The major product, 10-methylanthronyl-9-methyl ether, was formed by two successive alkylations. The first alkylation is at the C-10 carbon of anthrone yielding the sterically hindered intermediate, followed by a second deprotonation at the C-10 position and subsequent preferential alkylation at oxygen (Scheme 4). The monoalkylation of anthrone (2) with potassium hydroxide in a methanolic solvent system was demonstrated by Oki⁴⁹ to yield (21) in 86% yield (Scheme 16).

Two significant modifications to the anthrone alkylation process, the elimination of polar solvent(s) or reaction product(s) prior to the addition of the alkylating reagent and the utilization of lithium methoxide as the base significantly increased product yield of C-10 dialkylated anthrones. The addition of toluene to a basic methanolic reaction solution was followed by removal of the lower boiling polar solvent (MeOH) by distillation. Next, the alkyl bromide was added thus forming the desired product⁵⁰ (Scheme 17). Lithium methoxide was used to form the C-10 lithium salt of anthrone. Scheme 17 depicts one of two C-10 spirocycloanthrone (entries 46, Table 5) derivatives⁵⁰ (22) formed while employing hydroxide or methoxide as the base and toluene as the reaction solvent (the second is entry 47, Table 5).

Scheme 16: C-10 Monoalkylation of Anthrone⁴⁹

Scheme 17: C-10 Dialkylation of Anthrone⁵⁰

The significant improvement in yield and purity was a direct result of the two modifications described above. The degree of covalent bond formation between oxygen and lithium cation is considerably greater than between an oxygen and potassium cation (when potassium hydroxide is employed as a base). In addition, the removal of polar, hydroxylated solvents such as methanol and water (as product) substantially reduces the degree of solvation for both the counter cation and the monoalkylated anthrone anion (through hydrogen bonding of the alkoxide with the solvent). Both of these modifications result in a stronger oxygen cation bond of significantly greater covalent bond character, thus permitting the more basic C-10 carbon of the monoalkylated anthrone anion to react preferentially with the alkylating agent. In addition, the lithium cation may serve as a physical barrier to the alkylating reagent. The result is the formation of the thermodynamically favored C-10 dialkylated anthrone.

Efficient C-10 dialkylation reactions in the presence of water have recently been demonstrated under phase transfer catalysis (PTC) conditions. Combinations of 30% aqueous sodium hydroxide, an equal volume of methylene chloride, benzyl triethyl ammonium chloride, anthrone^{51,52} and an alkyl iodide can be stirred at room temperature to form 10,10-dialkylated anthrone derivatives in high yield. If the reaction is carried out with initial mono-

alkylation of anthrone and the product isolated, followed by a second alkylation reaction then non-equivalent alkyl group can be incorporated at the C-10 position of anthrone. The anthrone anion can react with a wide variety of allylic and propargylic bromides; reported yields range from 50 - 100% of the desired 10-mono- or 10,10-dialkylated product. The reaction occurs in the nonpolar solvent system, methylene chloride. By coulombic forces, benzyl triethyl ammonium and oxygen are mutually attracted thus sterically preventing O-alkylation and leading to preferential C-10 dialkylation of the monoalkylated anthrone enolate anion.

The organic soluble cation of the PTC catalyst, benzyl triethyl ammonium, solubilizes the hydroxide anion in the methylene chloride. The nucleophilicity of the hydroxide anion is increased in the organic solvent and the regioselectivity is improved. The reaction has been efficiently demonstrated with relatively small, moderately branched alkylating reagents (Scheme 18).^{51,52} Minimal O-alkylated products such as anthronyl-9-ethers have been reported when this PTC methodology is employed. One important relationship must be kept in mind; as the steric bulk of alkylating reagent increases, especially α to the carbon-bromine bond, the yield of desired dialkylated product decreases and 9-anthronyl ether formation increases.

Scheme 18: Dialkylation of Anthrone via Phase Transfer Catalysis^{51,52}

Control of regioselectivity of hydroxide/alkoxide promoted alkylation reactions of anthrone are often desired. Despite significant improvement of yields, this method of alkylation has been limited to dialkylation of anthrone and has not been employed effectively for the synthesis of 10-spirocycloanthrone formation.⁵⁰ The hydroxide/alkoxide method of preparation is significant as it is synthetically straightforward. Table 5 contains a summary of reactions.

**Table 5. Preparation of C-10 Anthrone Derivatives via Hydroxide/
Methoxide Alkylation Reaction Conditions to Form Carbon-
Carbon Bonds**

Substrate Employed, Anthrone			Entries 38 - 52			
<u>Entry</u>	<u>Product</u>	<u>Conditions</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
38	10,10-Dimethyl-anthrone	MeI/KOH aq. reflux	0 - 3	0	53, 54	NA
39	10,10-Diethyl-anthrone	EtI/KOH aq.	NA	0	54 - 55	NA
40	10,10-Dibenzyl-anthrone	Benzyl chloride KOH aq. reflux	NA	0	53	NA
41	10,10-Benzhydryl anthrone	Benzhydryl chloride/KOH	NA	0	41	NA
42a	10-Isoamyl-anthrone	Isoamyl iodide KOH aq. reflux	NA	0	57	NA
b	10,10-Dipropyl-anthrone	<i>n</i> -Propyl iodide KOH aq. reflux	NA	0	57	NA
43	10-(<i>o</i> -chlorobenzyl) anthrone	<i>o</i> -Chlorobenzyl chloride/KOH aq. reflux	NA	0	58	NA
44	10-Propargyl-anthrone	Propargyl bromide 90% EtOH/KOH	60	0	59	NMR/IR
45	10-[2-(1-Methoxycarbonylpropyl)] anthrone	2-Bromopropionate/MeOH/KOH/RT	86	0	49	NMR

<u>Entry</u>	<u>Product</u>	<u>Conditions</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
46		1) LiOMe 2) 2,3-Bis-(bromomethyl) naphthalene	80	0	50	NA
47		1) LiOMe 2) 1,8 Bis-(1-bromomethyl) naphthalene	25	0	50	NA
48	10,10-Dimethyl anthrone	1) LiOMe 2) 10 equiv MeI <i>t</i> -butanol/heat	70	0	60	NA
49	10,10-Dibenzyl anthrone	1) LiOMe 2) Benzyl chloride <i>t</i> -Butanol	23	0	57	NA
50	10,10-Diallyl anthrone	1) LiOMe/MeOH 2) toluene 3) allyl bromide	86 (crude)	0	61	IR

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
51	Anthrone	Phase Transfer Catalysis(benzyl triethylammonium chloride)/25 mL NaOH (30%)/ 25 mL CH ₂ Cl ₂ + R-Br (3 equiv)	10,10-Dialkyl- anthrone R ₁ = R ₂	see below	0	98	NMR/IR
a	Anthrone	as above	R = CH ₂ -CH=CH ₂	100	0	98	NMR/IR
b	Anthrone	as above	R = CH ₂ -CH=CH-CH ₃	100	0	98	NMR/IR
c	Anthrone	as above	R = CH ₂ -C≡C-CH ₃	90	0	98	NMR/IR
d	Anthrone	as above	R = CH ₂ -C≡C-CH ₂ - OC ₆ H ₄ -p-Cl	70	0	98	NMR/IR
e	Anthrone	as above	R = C(Me) ₂ -C≡CH (monoalkyl product)	50	0	98	NMR/IR
f	anthrone or 10-propargyl- anthrone	mono- or dialkylated product	R ₁ = R ₂ = CH ₂ -C≡CH	95	0	99	NMR/IR
g	anthrone or 10-propargyl anthrone	mono- or dialkylated product	R ₁ = CH ₂ -C≡CH R ₂ = CH(Me)-C≡CH	60	0	99	NMR/IR

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
h	10-propargyl-anthrone	KOH (1 eq.) aq. EtOH (90%) BrCH ₂ -C≡CH ₂	10-Dialkylanthrone R ₁ = CH ₂ -C≡CH ₂ R ₂ = CH ₂ -C≡CH	60	0	99/100	NMR IR
i	10-propargyl-anthrone	KOH (1 eq.) aq. EtOH (90%) Br-CH ₂ C ₆ H ₅	10-Dialkylanthrone R ₁ = Benzyl R ₂ = CH ₂ -C≡CH	55	0	99/100	NMR IR
52	Anthrahydroquinone dianion	Reaction with in situ quinone methide (QM) (from structure below)	10-Hydroxy-(10-benzyl derivatives) of anthrone	see below		101	MS/IR ¹ H NMR ¹³ C NMR
<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;"> <p>Alkylating reagent to a basic solution 1.3 equiv of substrate/60 °C 1-3 h</p> </div> <div style="text-align: center;"> </div> </div>							
a	Anthrahydroquinone dianion	R ₁ = R ₂ = R ₃ = H Y = Ac, X = Cl	R ₁ = R ₂ = R ₃ = Y = H	85	0	101	as above

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
b	Anthrahydroquinone dianion	R ₁ = R ₃ = H, R ₂ = OMe, Y = Ac, X = Cl	R ₁ = R ₃ = H, R ₂ = OMe, Y = H	85	0	101	MS/IR ¹ H NMR ¹³ C NMR
c	Anthrahydroquinone dianion	R ₁ = R ₂ = X = Cl, R ₃ = H, Y = Ac,	R ₁ = R ₂ = Cl, R ₃ = H, Y = H	70 (crude)	0	101	as above
d	Anthrahydroquinone dianion	R ₁ = R ₃ = H, R ₂ = OMe, X = Cl, Y = Ac	R ₁ = R ₃ = H, R ₂ = OMe, Y = H	10	0	101	as above
e	Anthrahydroquinone dianion	R ₁ = H, R ₂ = OMe, R ₃ = Me, X = Cl, Y = Ac	R ₁ = H, R ₂ = OMe, R ₃ = Me, Y = H	25	0	101	as above
f	Anthrahydroquinone dianion	Benzyl chloride instead of quinone methide	10-Hydroxy-10-benzyl anthrone	60	0	101	as above
g	Anthrahydroquinone dianion	Methyl vinyl ketone	10-Hydroxy-10-(Butyl-3-one) anthrone	54	0	101	as above
h	Anthrahydroquinone dianion	Cinnamaldehyde	10-Hydroxy-10-(1-phenylpropyl-3-al) anthrone (equilib. with lactone form)	41	0	101	as above

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
i	anthrone (1 eq.)	4 eq. HO ⁻ /QM (1 eq.) precursor from above R ₁ = R ₂ = R ₃ = H, Y = Ac, X = Cl	10-Hydroxy-(10- benzyl-derivatives) anthrone from above R ₁ = R ₂ = R ₃ = Y = H + 10,10-di-(4'-Hydroxy- benzyl)anthrone	NR	0	101	MS/IR ¹ H NMR ¹³ C NMR
j	anthrone (1 eq.)	same as entry (i, above) except 2 equiv QM	10,10-di-(4'-Hydroxy- benzyl)anthrone	98	0	101	as above

Formation of 10-Mono- and 10,10-Dialkylated Anthrones with Alkyl and Aryl Group(s) Incorporated in the Starting Material

The application of acids, Bronstead or Lewis, to form C-10 anthrone carbon-carbon bonds are highly efficient and well-documented reactions. The application of strong mineral acids to the generalized hydroxylated compounds⁶³⁻⁶⁸ **23A** and **24A** (Scheme 19), results in the formation of strong electrophiles in solution. These intermediates then undergo intramolecular cyclization reactions with aromatic ring systems within the substrate. The products formed, **23B** and **24B**, have been isolated in yields as high as 98%. In the case of **23B** ($Y = CH_2$), the 10,10-dialkyl-9,10-dihydroanthracene was subjected to chromium trioxide oxidation to yield 10,10-dialkylanthrone, **24B**. The chromium trioxide oxidizes the sensitive benzhydrylic carbon to yield a ketone. In addition, oxidation of **23B** ($Y = CH_2$, 10,10-dialkyl-9,10-dihydroanthracene) has typical yields of only 60 to 70%. These acid catalyzed cyclization reactions are redox neutral reactions. This mode of synthesis, while efficient, has only infrequently been used for the preparation of C-10 dialkyl/aryl anthrones, undoubtedly because the starting materials are not readily available.

Paralleling the synthesis of anthrone, Friedel-Crafts reactions have been employed extensively to form 10-alkyl-10-aryl and 10,10-diaryl-anthrones.

Aluminum(III) chloride has been the sole Lewis acid catalyst used to prepare these C-10 mono- and diaryl anthrones. Coordination of the Lewis acid with the halogen(s) of 10-haloanthrone results in nucleophilic attack by the solvent system, benzene⁶⁹⁻⁷¹ (Scheme 20). Alternatively, this may be viewed as an electrophilic substitution on the benzene ring. The substrate may be monohalogenated (25/27) or dihalogenated (29) and yield 10-aryl- or 10,10-diarylanthrone products (26 and 28, respectively; Scheme 20). The only nucleophiles employed to date have been the solvents: benzene, toluene, and N,N-dimethyl aniline.

Two unusual reports yielding C-10 substituted anthrones have been included in this section. The syntheses employ either anthraquinone⁷¹ or anthrone⁷² as the substrate in conjunction with excess aluminum(III) chloride and an aromatic solvent system. The proposed product is the 10-aryl- and 10,10-diaryl derivatives of anthrone (entry 68 a - f, Table 6). The claims made within these papers are unreasonable because net oxidation is occurring with no oxidizing reagent present but the data are included within this thesis for the sake of completeness.

Scheme 19: Generalized Synthesis of C-10 Substituted Anthrones via Acid Catalyzed Cyclodehydration Reactions⁶³⁻⁶⁸

Scheme 20: Friedel-Crafts Arylation Reactions with 10-Haloanthrones or Related Derivatives

Table 6: Friedel-Crafts and Acid Catalyzed Cyclodehydration Reactions to Yield 10-Alkyl or 10-Aryl Substituted Anthrones
Entries 53 - 75

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
53	10-Bromoanthrone	AlCl ₃ /C ₆ H ₆	10-Phenylanthrone	NA	-2	69	NA
54	10-Bromoanthrone	AlCl ₃ /Toulene	10-Tolylanthrone	NA	-2	69	NA
55	10-Chloro-10-phenyl-anthrone	AlCl ₃ /C ₆ H ₆	10,10-Diphenyl-anthrone	NA	-2	69	NA
56	10,10-Dichloro-anthrone	AlCl ₃ /C ₆ H ₆	10,10-Diphenyl-anthrone	NA	-4	69	NA
57	Phthalyl choride	AlCl ₃ /C ₆ H ₆	10,10-Diphenyl-anthrone	NA	-2	69	NA
58	Triphenylmethane-2-carboxylic acid	H ₂ SO ₄	10-Phenylanthrone	NA	0	73	NA
59	3,3-Diphenyl-phthalide	AlCl ₃ /C ₆ H ₆	10,10-Diphenyl-anthrone	NA	0	74	NA
60	10-Chloro-10-phenyl-anthrone	AlCl ₃ /Toluene heat	10-Phenyl-10-tolyl-anthrone	NA	-2	75	NA
61	10,10-Dichloro-anthrone	AlCl ₃ /Toluene	10,10-Ditolylanthrone	NA	-4	75	NA

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
62	10-Chloro-10-phenyl-anthrone	AlCl ₃ /N,N-dimethyl aniline	10-Phenyl-10-(p-di-Me aminophenyl)anthrone	NA	-2	76	NA
63	Anthraquinone	AlCl ₃ /N,N-dimethyl aniline	10,10-(p-dimethyl aminophenyl)-anthrone	NA	-4	72	NA
64	Anthrone	AlCl ₃ /C ₆ H ₆	10-Phenylanthrone	NA	0	71	NA
65	Anthrone	AlCl ₃ /Toluene	10-Tolylanthrone	NA	0	71	NA
66	Anthrone	AlCl ₃ /C ₆ H ₅ Cl	10-(4'-chlorophenyl)-anthrone and 10-Phenylanthrone	65.8 22.0	0	71	NA
67	Anthrone	AlCl ₃ /C ₆ H ₅ Br	10-(4'-bromophenyl)-anthrone and 10-Phenylanthrone	57.3 22.2	0	71	NA
68	Anthrone	AlCl ₃ /Anisole	10-(4'-methoxy phenyl) anthrone and 10-(4'-hydroxy phenyl) anthrone	60.0 14.0	0	71	NA

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
69		1) PPA/in vacuo heat 2) chromic anhydride	10-(Trichloro- methyl) anthrone	36	NA	63	NA
70	10-Chloro-10-ethyl anthrone	$\text{AlCl}_3/\text{C}_6\text{H}_6$	10-Ethyl-10-phenyl anthrone	85	-2	67	NMR/ IR
71		1) H_2SO_4 2) CrO_3 or 1) H_2SO_4 2) Br_2/CCl_4 3) aq. work up	10,10-Dimethyl anthrone	NR and 69	NA	64, 65	NMR/ MS
72	Triphenylmethane-2-carboxylic acid	H_2SO_4	10-Phenylanthrone	NA	0	66	NA
73	2,2-Dimethyl tri-phenyl methanol	1) KMnO_4 2) H_2SO_4	10-(2-Carboxylic acid phenyl) anthrone	NA	0	68	NA
74	10-(2-Carboxylic acid phenyl) anthrone	Sn/HCl reflux	10-(2-Carboxylic phenyl) lactone anthrone	NA	+2	68	NA
75	1,1-Diphenylethane-2-carboxylic acid	H_2SO_4	10-Methylanthrone	58	0	67	NA

Anthrone C-10 Carbon-Carbon Double Bond Formation

The formation of carbon-carbon at the C-10 position of anthrone will be reviewed, including bianthrone and bianthrylidene formation. The simplest of this class of compounds is 10-methyleneanthrone, **30** (Scheme 21). 10-Methyleneanthrone has an exocyclic C-10 carbon-carbon double bond ($R = H$, Scheme 21) and is the only room temperature stable quinone methide isolated to date. This compound is an important substrate for numerous reactions found in the remainder of this thesis. It has been reported that the exocyclic bond of **30** undergoes nucleophilic attack by phenyl magnesium bromide,⁷⁷ can add bromine across the double bond to form 10-bromo-10-bromomethylanthrone,⁷⁸ and has been used extensively to prepare 10-spirocyclopropylanthrone and other 10-spirocycloanthrone derivatives.⁸⁰⁻⁸² Due to the numerous phenyl ring substitution patterns available and the ease of synthesis, a great many derivatives of 10-benzylideneanthrone derivatives (**31**, Scheme 21) have been

Scheme 21: 10-Methyleneanthrone and 10-Benzylideneanthrone

prepared. The formation of a carbon-carbon double bond at the C-10 position of anthrone has been accomplished by a variety of methodologies. Within this section, these reactions can be categorized as (a) condensation with aldehydes under basic⁸²⁻⁹⁷ or acidic reaction conditions,^{40,98-103} (b) dehydration of 10-hydroxy-10-alkyl-anthrone,^{87,88,115} (c) reaction with benzaldehyde and organometallic derivatives of anthrone (**33**, Scheme 22 (a - c)),⁹⁶ and (d) base induced nucleophilic attack on carbon disulphide^{104,105} (**34**, Scheme 23).

Both the acid and base catalyzed condensation reactions of aldehydes, especially benzaldehydes, with the active methylene group of anthrone has been the predominant method of C-10 carbon-carbon double bond formation. In each of the cases outlined above, anthrone acts as the nucleophile. The initial step with either the acid or base catalyzed aldehyde condensation reaction is the formation of the anthronyl anion (reaction with base) or anthranol (acid catalyzed reaction). These species are in equilibrium with their respective keto resonance forms. In an aldol-like reaction, anthrone reacts with the aldehyde to form an alcohol, **35**, that is subsequently dehydrated (**35** to **36**, Scheme 24, base catalyzed reaction conditions). Note, base catalyzed condensation reactions generally proceed in greater yields than the equivalent acid-catalyzed reactions, as demonstrated by entry 83, Table 7.

Scheme 22: Formation of 10-Methyleneanthrone and Related Derivatives

In addition, formation of the exocyclic C-10 double bond from 10-hydroxy-10-alkyl (or benzyl) anthrone may occur in the presence of strong acids or spontaneously on distillation as with 10-ethyl-10-hydroxyanthrone with the simultaneous loss of water (entry 78, Table 7).

An unusual example of the nucleophilicity of the anion of anthrone is depicted in Scheme 23. Nucleophilic attack by anthrone anion, **20**, at the electropositive carbon atom of carbon disulfide forms a -CS_2^- group. A second equivalent of base then deprotonates the C-10 monosubstituted anthrone which is followed by the formation of a =CS_2^{2-} group. This dianion is reacted twice with an alkylating reagent, forming the geminol disulfide (Scheme 23, entries 95 and 96, Table 7).

Scheme 23: C-10 Geminol Disulfide Anthrone Formation

Three of the most common side products isolated from anthrone reactions, especially prevalent prior to the use of inert atmospheric reaction conditions, were anthraquinone (**1**), bianthrone (**37**) and bianthrylidene (**38**). The formation of these side products can result from air oxidation of anthrones, even under simple reflux conditions or on isolation of the products. Oxygen is capable of initiating the formation of anthrone free radical intermediates that ultimately recombine to form compounds **1** and **37**, above.

The formation of bianthrone (**37**) from anthrone, is a redox neutral reaction according to the “functional group family” definition used throughout this thesis. Nevertheless, by the more traditional definition of oxidation states of carbon atoms, the dimerization of anthrone to **37** is a 2-electron oxidation and the conversion to **38** is a 4-electron oxidation. Table 8 contains a summary of the reactions that intentionally yield **37** and **38** as products. These particular compounds, **37** and **38** have had very few published synthetic applications. Examples of common reaction conditions used to prepare **37** and **38** can be found in Scheme 25. Bianthrone and bianthrylidene reactions can be found in Table 8, all other C-10 carbon-carbon double bond forming reactions are found in Table 7.

Scheme 24: Anthrone C-10 Carbon-Carbon Double Bond Formation

Scheme 25: Bianthrone (37) and Bianthrylidene (38) and Reaction Conditions to Form 37 and 38

37

38

2

37

Table 7: Carbon-Carbon Double Bond Formation at the C-10 Position of Anthrone
Entries 76 -109

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
76	Anthrone	NaOH/CH ₂ O aq.	10-Methylene-anthrone	NA	0	82	NA
77	Anthrone	CH ₂ O/MeOH or EtOH/piperidine	10-Methylene-anthrone	NA	0	83, 84	NA
78	10-Ethyl-10-hydroxy anthrone	Distillation/N ₂	10-Ethylidene-anthrone	NA	-2	85	NA
79	Anthrone	Crotonaldehyde/ base	10-Crotonylidene-anthrone	NA	0	86	NA
80	Anthrone	<i>m</i> -Nitrobenz-aldehyde/ piperidine	10-(<i>m</i> -Nitrobenzylidene)-anthrone	75	0	87	NA
81	Anthrone	Pyridine/reflux piperidine/ benzaldehyde	10-Benzylidene-anthrone	65	0	87- 89	NA
82	Anthrone	Pyridine/reflux piperidine/ anisaldehyde	10-Anisylidene-anthrone	72	0	90- 91	NA

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
83	Anthrone (2) + substituted benzaldehyde	Acidic: acetic anhydride reflux Basic: Pyridine/ piperidine/reflux		Recorded as acidic (A) and basic (B) reaction conditions	0	92	IR
<u>Phenyl Substituent</u>							
a	(2) + substituted benzaldehyde	acid or base reaction	H	A: 69 B: 78	0	89, 92	IR
b	(2) + substituted benzaldehyde	acid or base reaction	2-OH	A: 26 B: 33	0	92	IR
c	(2) + substituted benzaldehyde	acid or base reaction	4-OMe	A: 65 B: 83	0	89, 92	IR
d	(2) + substituted benzaldehyde	acid or base reaction	3,4-O ₂ -CH ₂ -	A: 48 B: 56	0	92	IR
e	(2) + substituted benzaldehyde	acid or base reaction	4-N(Me) ₂	A: 20 B: 21	0	92	IR

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
83f	Anthrone (2) + substituted benzaldehyde	Acidic: acetic anhydride reflux Basic: Pyridine/ piperidine/reflux	2-NO ₂	A: 54 B: 65	0	92- 94	IR
g	(2) + substituted benzaldehyde	acid or base reaction	2-OMe; 3,4-OH	A: 29 B: 37	0	92	IR
h	(2) + substituted benzaldehyde	acid or base reaction	2-OMe; 3,4-OAc	A: 26 B: 30	0	92	IR
i	(2) + substituted benzaldehyde	acid or base reaction	4-Me	A: 18 B: 27	0	92	IR
j	(2) + substituted benzaldehyde	acid or base reaction	4-NO ₂	A: 43 B: 59	0	92	IR
84	Anthrone + aldehyde or ketone	Reflux 3 h/ MeOH or EtOH HOAc (1 drop)		see below	0	95	IR

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
84a	as above	as above	R = CH(C ₆ H ₅)	55	0	95	IR
b	Anthrone + aldehyde or ketone	Reflux 3 h/ MeOH or EtOH HOAc (1 drop)	R = C(Me) ₂	60	0	95	IR
c	Anthrone + aldehyde or ketone	as above	R = C(Me) ₁ (C ₆ H ₅) ₁	60	0	95	IR
d	Anthrone + aldehyde or ketone	as above	R = (CH-3-furanyl)	40	0	95	IR
e	Anthrone + aldehyde or ketone	as above	R = (CH-CH=CH-C ₆ H ₅)	50	0	95	IR

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
85		4 equiv. substituted benzaldehyde (Ar-CHO)/reflux 8 to 12 h	Substituted 10- benzylideneanthrone	see below	0	95	IR(NR) NMR(NR)
		Substitution of Ar-CHO indicated under <u>Product</u>					
a	as above	as above	R = H	50	0	95	See above
b	as above	as above	R = 3-NO ₂	70	0	95	See above
c	as above	as above	R = 4-NO ₂	90	0	95	See above
d	as above	as above	R = 4-Cl	60	0	95	See above
e	as above	as above	R = 3-Me	50	0	95	See above
f	as above	as above	R = 4-Me	60	0	95	See above
g	as above	as above	R = 4-OMe	50	0	95	See above
i	as above	as above	R = 3,4-(OMe) ₂	40	0	95	See above
j	as above	as above	R = 3,4-(OMe) ₂ ; 6-Br	35	0	95	See above
k	as above	as above	R = 2-(furanyl)	50	0	95	See above
l	as above	as above	R = (=CH-CH=CH-C ₆ H ₆)	60	0	95	See above

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
86a	Anthrone	C ₆ H ₆ - CH=C(CO ₂ Me) ₂ / piperidine	10-Methyl-10- benzalmalonate- anthrone	NR	0	97	NA
b	Anthrone	C ₆ H ₆ - CH=C(CO ₂ Me) ₁ (CO ₂ Et) ₁ / piperidine	10-Ethyl-10- benzalacetate anthrone	NR	0	97	NA
87	10-Hydroxy-10- benzyl anthrone	H ₂ SO ₄ /70 °C	10-Benzylidene- anthrone	NA	-2	98	NA
88	Anthrone	HCl gas/ Benzaldehyde	10-Benzylidene- anthrone	NA	0	99	NA
89	10-Hydroxy-10- benzyl anthrone	H ₂ SO ₄ /heat	10-Benzylidene- anthrone	50	-2	100	NMR/IR MS
90	10-Hydroxy-10- benzyl anthrone	HCl/AcOH 100 °C	10-Benzylidene- anthrone	NA	-2	87,88 100	NA
91	Anthrone	Chloral/ZnCl ₂	10,10-(1,2-ethane- diylidene)dianthrone	60	0	101	NA
92a	Anthrone	Malononitrile/ SOCl ₂	10-Dicyanomethylene anthrone	88	-4	40	NA

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
92b	10-Dicyano-methylene anthrone	20 mL H ₂ SO ₄ 2 mL H ₂ O		42	0	40	NA
c	Product 86b above	EtOH/H ₂ gas Pd/C (5%)		60	0	40	NA
d	10-Dicyano-methylene anthrone	Toluene/H ₂ gas Adams Catayst	10-(1,1-Dicyano-methyl) anthrone	80	0	40	NA
93		150 °C/HCl/2 h substituted benzaldehyde (Ar-CHO as follows)	10-Substituted benzylidene anthrone (substitution as follows)	see below	0	102	NMR/IR MS
a	Anthrone	R = H	R = H	NR	0	102	NMR/IR MS
b	Anthrone	R = 2-OMe	R = 2-OMe	NR	0	102	NMR/IR

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
d	Anthrone	R = 2-OMe	R = 2-OMe	80	0	102	NMR/IR MS
e	Anthrone	R = 2,4-OMe	R = 2,4-OMe	80	0	102	NMR/IR MS
f	Anthrone	R = 2,4,6-OMe	R = 2,4,6-OMe	80	0	102	NMR/IR MS
g	Anthrone	R = 2,4,6-Me	R = 2,4,6-Me	46	0	102	NMR/IR MS
94	2,3-Dichloro-2,3-diphenyl indanone	H ₂ SO ₄	10-(1-Chloro-benzylidene) anthrone	NR	0	103	NA
95	Anthrone	DMSO + 1) KOH/H ₂ O 2) CS ₂ 3) Me ₂ SO ₄		NA	0	104	NR
96	Anthrone	DMSO + 1) KOH/H ₂ O 2) CS ₂ 3) Cl ₂ CHCO ₂ Et		NA	0	105	NR

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
97	Anthrone	C ₆ H ₄ N(3)/ HOAc (1)/reflux 4 hr. 1.2 equiv below		see below	0	106	NA
		I ⁻					
a	Anthrone	as above	X = S, R = H	85	0	106	NMR/IR MS
b	Anthrone	as above	X = S, R = Me	88	0	106	NMR/IR MS
c	Anthrone	as above	X = Se, R = H	86	0	106	NMR/IR MS
98	Anthrone (2)	1) AlCl ₃ /CH ₂ Cl ₂ -50 °C/tetrachloro- cyclopropene (1 eq.) + 2 equiv of cyclopropene reagent (R ₁ /R ₂) 2) Reflux with 2 (1 equiv) CHCl ₃		see below	0	106	NMR/IR MS

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
98a	Anthrone	$R_1 = R_2 = 4'-(2,6\text{-di-}t\text{-butyl phenol})$	$R_1 = R_2 = 4'-(2,6\text{-di-}t\text{-butyl phenol})$	75%	0	107	NMR/IR MS
b	Anthrone	1) $R_1 = (2 \text{ equiv})$ 9-MeO-anthracene 2) $R_2 = (1 \text{ equiv})$ 4'-(2,6-di- <i>t</i> -butyl phenol) instead of (2) 3) $\text{BBr}_3/\text{CHCl}_3$	$R_1 = (9\text{-HO-anthryl})$ $R_2 = 4'-(2,6\text{-di-}t\text{-butyl phenol})$	79	0	107	NMR/IR MS
c	Anthrone	1) $R_1 = R_2 = (2 \text{ eq.})$ 9-MeO-anthracene 2) not performed 3) $\text{BBr}_3/\text{CHCl}_3$	1,2-Bis(9-hydroxy-10-anthryl) cyclopropanone	83	0	107	NMR/IR MS
d	98, entry b product	Note: entries b, c above convertible to keto form with $\text{K}_3\text{Fe}(\text{CN})_6$ or PbO_2 1) entry 98b, keto form	2,3-Bis(9-oxo-10-anthrylidene) cyclopropanone	93	0	107	NMR/IR MS

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF Ref.</u>	<u>Spectra</u>
98e	98, entry d product	CH ₂ Cl ₂ /UV (loss of CO gas)	Dianthraquino-ethylene	75	0	107 NMR/IR MS
		above entry 98d keto compounds convertible to enol form with Sn/HCl				
99		R = C ₆ H ₅ , FeCl ₃ /(Me ₃) ₃ COH or R = C ₃ H ₇ , FeCl ₃ /MeOH		90.2 and 83.0	0	108-110 NMR /IR
100	Anthrone	Glyoxol sulfate AcOH/0.5 hr. reflux		NR	0	111 NA

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
101	Anthrone	Terephthalaldehyde		NR	0	111	NA
102	10-(1,1-Dichlorobenzyl) anthrone	Pyridine/heat	10-(1-Chlorobenzylidene) anthrone	NA	0	112	NA
103	Anthrone			O = 21 S = 27 SO ₂ = 11	-2	113	NA

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
104a	Anthrone			38	-2	113	NA
b	Anthrone	R = C ₆ H ₅	R = C ₆ H ₅				
c	Anthrone	R = C ₆ H ₄ - <i>p</i> -Cl as above	R = C ₆ H ₄ - <i>p</i> -Cl as above	62	-2	113	NA
104d	Anthrone	R = C ₆ H ₄ - <i>o</i> -Cl as above	R = C ₆ H ₄ - <i>o</i> -Cl as above	12	-2	113	NA
f	Anthrone	R = C ₆ H ₄ - <i>p</i> -OMe as above	R = C ₆ H ₄ - <i>p</i> -OMe as above	23	-2	113	NA
		R = C ₆ H ₄ -3,4- O ₂ CH ₂ as above	R = C ₆ H ₄ -3,4- O ₂ CH ₂ as above	25	-2	113	NA
105a	10-Methylene anthrone	(EtO) ₃ CH/Aniline 1 eq. each	10-(1-Anilino- methylene) anthrone	88	0	114	NA

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
105b	10-(1-Anilino methylene) anthrone	2 N KOH/RT	10-(1-Hydroxy-methylene) anthrone	12	0	114	NA
106a	10-Hydroxy-10-butyl anthrone	AcOH/H ₂ SO ₄	10-(1-Butylidene) anthrone	48	-2	115	NA
b	10-Hydroxy-10-isoamyl anthrone	cold H ₂ SO ₄	10-(1-Isoamylidene) anthrone	NA	-2	115	NA
107a	10-(1-Chloro methylene)-anthrone	NaN ₃ (2.5 equiv) DMF	10-(1-Azido-methylene) anthrone	94 (crude)	0	102	IR/MS NMR
b	10-(1-Bromo methylene)-anthrone	KCN 95% DMF 5% H ₂ O	10-(1-Cyano-methylene) anthrone	20	0	102	IR/MS NMR
c	10-(1-Bromo-benzylidene)-anthrone	KCN 95% DMF 5% H ₂ O	10-(1-Cyano-benzylidene) anthrone	20	0	102	IR/MS NMR
d	10-(1-Chloro methylene)-anthrone	NaOMe MeOH or DMF	10-(1-Methoxy-methylene) anthrone	54	0	102	IR/MS NMR
e	10-(1-Chloro methylene)-anthrone	PdCl ₂ /AcOH/ NaOAc/65° C	10-(1-Acetoxy-methylene) anthrone	54	0	102	IR/MS NMR

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
f	10-(1-Chloro-methylene)-anthrone	Aniline	10-(1-Anilino-methylene) anthrone	80	0	102	IR/MS NMR
g	10-(1-Bromo-methylene) anthrone	Aniline	10-(1-Anilino-methylene) anthrone	89	0	102	IR/MS NMR
h	10-(1-Bromo-benzylidene)-anthrone	KCN 95% DMF 5% H ₂ O	10-(1-Cyano-benzylidene)-anthrone	39	0	102	IR/MS NMR
108	Anthrone	Anisaldehyde/ piperidine/ pyridine	10-Anisylidene anthrone	72	0	90	IR/MS UV/NMR
109	Anthrone	Diphenyl- dichloromethane	10-Benzhydrylidene anthrone (Anthrafuchstone)	NA	0	87, 116, 117	NA

Table 8: Formation of Bianthrone and Bianthrylidene Entries: 110 - 125

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
110	Anthrone	Xylene reflux	10,10-Bianthrone	NA	0	118	NA
111	Anthrone	FeCl ₃ /AcOH	10,10-Bianthrone	NA	0	119	NA
112	Triphenyl carbinol	ZnCl ₂	10,10-Bianthrone	NA	0	120	NA
113a	Anthrone	Ultrasound/FeCl ₃ solid state/RT/6h	10,10-Bianthrone	82	0	121	NA
b	Anthrone	Ultrasound/FeCl ₃ solid state/6h t = 50 °C	10,10-Bianthrone	97	0	121	NA
114	Anthrone	FeCl ₃ /solid state t = 50 °C	10,10-Bianthrone	77	0	121	NA
115	Anthrone	N-Chlorosuccin- imide/triethyl amine/CH ₂ Cl ₂	10,10-Bianthrone	75	0	122	NA
116	Anthrone	Zn/AlCl ₃ , CH ₃ CN Ultrasound	10,10-Bianthryl- idene	75	0	123	NA
117	10-Bromoanthrone	Cu powder	10,10-Bianthrone	NA	-4	124	NA

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
118	Anthrone	Di- <i>t</i> -butyl peroxide/reflux bromobenzene	10,10-Bianthrone	70	0	125 126	NA
119a	Triethyl ammonium-9-(10-acetoxyanthronyl) acetate	1) 28% aq. NH ₃ 2) NH ₄ Cl/CH ₃ CO ₂ H/H ₂ O	10-Hydroxy-10-sulfate-10,10-bianthrone	44	0	127	NA
b	10-Hydroxy-10-sulfate-10,10-bianthrone	KOH/H ₂ O/90 °C	10,10-Bianthrylidene	100	-4	127	NA
120	Anthrone	<i>p</i> -Tolylodiodifluoride CHCl ₃	10,10-Bianthrone	NR	0	128	NA
121	10,10-Bianthrone	<i>p</i> -Quinone	10,10-Bianthrylidene	NR	0	129	NA
122	Anthrone	CH ₂ N ₂ /ether	10,10-Bianthrone	90	0	130	NR
123	10,10-Bianthrylidene	Flourene/250 °C	10,10-Bianthrone + biffuorene	88	0	131	NA
124a	Anthraquinone	HCl/toluene/Zn/H ₂ O reflux	10,10-Bianthrone anthracene bianthrylidene	44 19 12	-4	132	NA

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
124b	1,2-Bis-(10-hydroxy-9-anthranyl) ethane	DDQ/dioxan/ heat		65	-4	132	NA
125	Anthrone	Azobenzene/ 100 °C/4 h	10,10-Bianthrone	80	0	133	NA

Formation of 10-Alkyl and Aryl Anthrones Including Derivatives Containing 10-Halo-, 10-Hydroxy-, 10-Nitro- and Additional Electron Withdrawing Functional Groups

This section has been divided into two parts with a common theme. The common theme is the preparation of C-10 alkyl or aryl derivatives of anthrone. The first section describes the formation of C-10 anthrone derivatives from substrates at or below a zero oxidation state. These substrates were subjected to alkylating reaction conditions. This was followed by oxidation of the intermediate to yield the desired product. The second section summarizes the preparation of 10-alkyl/aryl-10-heteroatom substituted anthrones. All of the reactions that form this class of C-10 disubstituted anthrones above can be catalogued as follows: (a) oxidation of 9,10-dialkyl/aryl-9,10-dihydroanthracenes derivatives, (b) functional group interconversion of 10-hydroxy-10-alkyl/aryl anthrones to 10-halo-10-alkyl/aryl anthrone derivatives (redox neutral reactions), (c) addition of halogen across the double bonds of 10-methylenanthrone and related derivatives, (d) preparation of 10-nitro- and 10-nitro-10-alkyl-anthrones, and (e) formation of 10-thioanthraquinone and related sulfide derivatives

Examples of 10-alkyl/aryl anthrone formation by oxidation of 10-substituted anthracenes and 9,10-di(alkyl/aryl)-9,10-dihydroanthracenes (section (a))

have been published. In 1905, Liebermann and Lindenbaum¹³⁴ prepared 10,10-diphenylanthrone from 10,10-diphenyl-9,10-dihydroanthracene and chromium trioxide and acetic acid solution. Other oxidizing reagents combined with anthracene or dihydroanthracene derivatives to prepare C-10 anthrone derivatives include bromine in carbon tetrachloride,^{135,136} hydroxide/hydrogen peroxide,^{137,138,171} sodium dichromate and acetic acid,^{139,140} chromium trioxide and acetic acid,^{134,141} and lead tetraacetate in acetic acid.^{142,143} While the oxidation of 10,10-di(alkyl/diaryl)-9,10-DHA reactions described above yield the desired product, the fundamental constraint of these reactions is the lack of good synthetic methods for the starting dihydroanthracenes, especially those with non-equivalent functional groups.

Perhaps the most exciting development concerning anthrone derivative preparation was the publication of two papers^{140,143} describing general syntheses for sterically hindered, non-equivalent C-10 dialkylated anthrones. The first paper, by Dalpozza et al.,¹⁴³ employed 9-nitroanthracene (**39**) as the substrate (Scheme 26). Addition of three equivalents of Grignard reagent resulted in nucleophilic attack at the C-10 position of 9-nitroanthracene. The intermediate (**40**) was stabilized by the electron withdrawing nitronate group and magnesium salt coordination with the nitronate functional group.

Combination of **40** and lead (IV) tetraacetate formed 10-alkyl-9-nitroanthracene, **41**. Isolation of product, **41**, and addition of a further three equivalents of Grignard reagent resulted in dialkylation at the C-10 position of the intermediate (**42**). The first and second additions of Grignard reagent(s) need not have identical functional groups. Combination of **42** and lead (IV) tetraacetate results in the formation of the desired 10,10-dialkylated anthrone (**43**, entry 129, Table 9). Yields from this series of reaction range from 64 - 84%.

This research included the only published preparation of 10-cyclohexyl-10-alkyl anthrone derivatives, an example that illustrates the versatility of this method for introducing branched alkyl groups at the C-10 position. This work is significant as even the smallest alkyl group, CH₃, would be forced to lie between the C-4/C-5 peri hydrogens of anthrone in a high energy state. The bulkier cyclohexyl group is located above the plane of the tricyclic ring system. Preparation of such sterically hindered anthrone derivatives has not yet been demonstrated with anthrone as the initial substrate. Although the overall yield for this series of reactions is low, it permits access to previously unreported sterically congested derivatives of anthrones.

The second paper, by Rabideau et al.,¹⁴⁰ also reported C-10 dialkylated anthrones with nonequivalent alkyl groups (Scheme 27). (Note, Rabideau did

not report attempts to prepare the same sterically congested dialkylated anthrone derivatives as Dalpozza). The substrate, 9,10-dihydroanthracene (9,10-DHA, **44**) was deprotonated at the C-9 carbon with butyllithium (BuLi) and then allowed to react with trimethylsilyl chloride (TMSCl) to yield **45**, (9-TMS-9,10-DHA). A second deprotonation at the C-10 position of the substrate (**45**) with 1.25 equivalents BuLi, followed by 1.5 to 2.0 equivalents of alkyl iodide yielded the 9-alkyl-9-TMS derivative, **46**. A third deprotonation of the central ring system with 1.25 equivalents of BuLi on the isolated compound **46** was preceded by a novel 1,4 TMS migration from the C-9 to the C-10 carbon of the DHA derivative. Addition of 1.5 to 2.0 equivalents of alkyl iodide yielded the 9-TMS-10,10-dialkyl-9,10-DHA, **47**. Oxidative cleavage of the TMS group with sodium dichromate and acetic acid solution yields the desired 10,10-dialkylanthrone, **43**.¹⁴⁰

Yields from the oxidation of the 9-TMS-10,10-dialkyl-9,10-DHA ranged from 87 - 90%, superior to the oxidative yields of 10,10-dialkyl-9,10-DHA of 60 - 70% with sodium dichromate and acetic acid solution described previously. Additional type **47** compounds were prepared but the TMS group was instead cleaved with tetrabutylammonium fluoride to yield 10,10-dialkyl-9,10-DHA derivatives.

Scheme 26: 10,10-Dialkylanthrone Synthesis From 9-Nitroanthracene¹⁴³

Scheme 27: 10,10-Dialkylanthrone Synthesis From 9,10-DHA¹⁴⁰

The formation of 10,10-dialkylated anthrones from 9,10-DHA and 9-nitroanthracene has been a crucial step in understanding the conformations of sterically congested anthrones and dihydroanthracenes as these syntheses permitted access to previously inaccessible derivatives. It was the general nature of these syntheses that permit preparation of a large number of novel C-10 dialkylated anthrones. These preparations may be employed with a wide variety of Grignard or alkyl iodide reagents.

An additional class of derivatives has been included in this section, preparation of C-10 alkyl/aryl anthrones that also possess hydroxy-, ether-, halogen-, nitro-, thioketo-, sulfide, or nitrogen based functional groups at the C-10 position. 10-Halo-10-alkyl/arylanthrones have been prepared by two predominant routes. In the first general synthetic route, either hydrochloric acid,^{99,144} hydrobromic acid,^{145,146} or phosphorus pentachloride¹⁴⁶⁻¹⁴⁹ was combined with 10-hydroxy-10-alkyl/arylanthrone (**48**) yielding the halogenated derivatives **49A/B** (Scheme 28). These series of reactions are simply redox neutral, functional group interconversions. In the second series of reactions, 10-benzylideneanthrone (**31**) or its derivatives were combined with either bromine,^{90,150} sulfural bromide or sulfural chloride.^{102,150} The action of these reagents was the addition of the halogen across the C-10 double bond to yield 10-halo-10-(1-halobenzyl)anthrone derivatives.

Scheme 28: Synthesis of 10-Halo Anthrones via Functional Group Interconversion of 10-Hydroxyanthrone

The preparation of 10-nitroanthrone and the 10-nitro-10-alkyl/aryl derivatives has been accomplished predominately by reacting 9-R-anthronyl derivatives (**50A**, R = acetyl¹⁵¹⁻¹⁵³; **50B**, R = methoxy^{151,152}; **50C**, R = acyl¹⁵¹) and the 10-alkyl/aryl derivatives of **50 A, B** or **C** with nitric/acetic acid solutions (Scheme 29). The reaction proceeds with cleavage of the functional group from the C-9 ether oxygen. The resulting anion (**51A/B**) nucleophilically attacks a nitronium cation, thus forming the 10-nitroanthrone or 10-alkyl/aryl derivative, **52** (Scheme 29). Other nitrating reagents used to prepare type **52** derivatives included nitrogen dioxide¹⁵⁴ and pyridium nitrate.¹⁵⁵ 10-Nitroanthrone and 10-alkyl/aryl-10-nitroanthrones have been isolated in yields as high as 80 percent (entries 143 - 148, Table 9).

Scheme 29: Generalized Synthesis of 10-Nitroanthrone Derivatives and Related Derivatives

Another series of novel anthrone derivatives, beginning with the synthesis of 10-thioanthraquinone, **53**,¹⁵⁶⁻¹⁵⁸ has been reported only in the past 20 years (Scheme 30). Synthesis of **53** has been reported by two methods. The first was a two electron oxidation of anthrone with dithiobisphthalimide in a basic solvent system. The yield was a moderate 37.5 percent.¹⁵⁶ The second reported synthesis of **53** combined diazoanthrone (**54**, DAAN) and sulfur in hot DMF.¹⁵⁸ This redox neutral reaction had a yield of 57 percent. In the presence of 2,3-dimethylbutadiene or cyclopentadiene, **53** was readily converted to the sulfide adducts **55**^{156,158} or **56**,¹⁵⁸ respectively, via Diels-Alder reactions. **56** reportedly decomposes above 22 °C (Scheme 30).

Table 9 contains a summary of related syntheses.

Scheme 30: Formation of 10-Thioanthraquinone and Related Derivatives

Table 9: Formation of 10-Alkyl/Aryl-10-Heteroatom Anthrone and Related Derivatives
Entries: 126 - 179

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
126	9-R-Anthracene	MeOH/CuBr ₂ Reflux	see below	see below	NA	159	NA
a	R = -C ₆ H ₅	MeOH/CuBr ₂ Reflux	10-Methoxy-10-phenylanthrone	61	+2	159	NA
b	R = <i>p</i> -MeO-C ₆ H ₄	MeOH/CuBr ₂ Reflux	10-Methoxy-10-(4'-methoxyphenyl)-anthrone	65	+2	159	NA
c	R = -Me	MeOH/CuBr ₂ Reflux	10-Methoxy-10-methylanthrone	25	+2	159	NA
d	R = -CH ₂ OMe	MeOH/CuBr ₂ Reflux	10-Methoxy-10-methoxymethyl-anthrone	6	+2	159	NA
e	R = -Et	MeOH/CuBr ₂ Reflux	10-Methoxy-10-ethylanthrone	60	+2	159	NA
f	R = - <i>i</i> -Pr	MeOH/CuBr ₂ Reflux	10-Methoxy-10-isopropylanthrone	NR	+2	159	NA
g	R = benzyl	MeOH/CuBr ₂ Reflux	10-Methoxy-10-benzylanthrone	NR	+2	159	NA

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
127	Anthracene	1) MeOH, 2 N NaOH/ electrolysis 2) TFA/TFAA	10,10-Dimethoxy- anthrone	21	+4	160	NMR/ MS
128	9,10-DHA	1) <i>n</i> -BuLi/TMScI 2) <i>n</i> -BuLi/R-I 3) <i>n</i> -BuLi/R'-I 4) Na ₂ Cr ₂ O ₇	10-R-10-R' anthrone	see below	+4	140	NMR/ MS
a	9,10-DHA	as above	R = R' = Me	90	+4	140	NMR/ MS
b	9,10-DHA	as above	R = R' = Et	81	+4	140	NMR/ MS
c	9,10-DHA	as above	R = R' = iPr	70	+4	140	NMR/ MS
d	9,10-DHA	as above	R = R' = Allyl	75	+4	140	NMR/ MS
e	9,10-DHA	as above	R = R' =Benzyl	90	+4	140	NMR/ MS
f	9,10-DHA	as above	R = Me, R' = Et	86	+4	140	NMR/ MS

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
128g	9,10-DHA	1) <i>n</i> -BuLi/TMSCl 2) <i>n</i> -BuLi/R-I 3) <i>n</i> -BuLi/R'-I 4) Na ₂ Cr ₂ O ₇	R = Et, R' = Me	85	+4	140	NMR/ MS
h	9,10-DHA	as above	R = Me, R' = <i>i</i> -Pr	76	+4	140	NMR/ MS
i	9,10-DHA	as above	R = Et, R' = <i>i</i> -Pr	70	+4	140	NMR/ MS
j	9,10-DHA	as above	R = Me, R' = Allyl	80	+4	140	NMR/ MS
k	9,10-DHA	as above	R = Me, R' = Benzyl	76	+4	140	NMR/ MS
129	9-Nitroanthracene	1) 3 equiv R-MgX 2) Pb(OAc) ₄ 3) 3 equiv R'-MgX 4) Pb(OAc) ₄	10-R-10-R' anthrone	see below	0	140	NMR
a	9-Nitroanthracene	as above	R = R' = Me	64	0	143	NMR
b	9-Nitroanthracene	as above	R = R' = (CH ₂) ₂ C ₆ H ₆	78	0	143	NMR

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
129c	9-Nitroanthracene	1) 3 equiv R-MgX 2) Pb(OAc) ₄ 3) 3 equiv R'-MgX 4) Pb(OAc) ₄	10-R-10-R' anthrone R = R' = <i>n</i> -C ₆ H ₁₃	68	0	143	NMR
d	9-Nitroanthracene	as above	R = <i>n</i> -C ₆ H ₁₃ , R' = Me	84	0	143	NMR
e	9-Nitroanthracene	as above	R = <i>c</i> -C ₆ H ₁₁ , R' = Me	74	0	143	NMR
f	9-Nitroanthracene	as above	R = (CH ₂) ₂ C ₆ H ₅ R' = <i>n</i> -C ₆ H ₁₃	71	0	143	NMR
130	10-Hydroxy-10-ethylanthrone	PCl ₅	10-Chloro-10-ethylanthrone	NA	0	147, 148	NA
131	10-Hydroxy-10-ethylanthrone	HCl gas/C ₆ H ₆	10-Chloro-10-ethylanthrone	NA	0	144	NA
132	10-Hydroxy-10-isobutylanthrone	PCl ₅	10-Chloro-10-isobutylanthrone	NA	0	146, 148, 149	NA
133	10-Hydroxy-10-isoamylanthrone	PCl ₅	10-Chloro-10-isoamylanthrone	NA	0	146-148	NA

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
134	10-Hydroxy-10-isoamylanthrone	HBr gas/C ₆ H ₆	10-Bromo-10-isoamylanthrone	NA	0	145	NA
135	10-Hydroxy-10-phenylanthrone	HBr/C ₆ H ₆	10-Bromo-10-phenylanthrone	NA	0	146	NA
136	10-Hydroxy-10-phenylanthrone	PCl ₅	10-Chloro-10-phenylanthrone	NA	0	148	NA
137	10-Hydroxy-10-phenylanthrone	PCl ₅ , CHCl ₃ or C ₆ H ₆	10-Chloro-10-phenylanthrone	NA	0	146	NA
138	<i>o</i> -Benzhydryl benzoic acid	SOCl ₂	10-Phenyl anthrone	NA	0	161	NA
139	10-Hydroxy-10-ethylanthrone	Br ₂ /AcOH	10-Bromo-10-(1-bromoethyl)anthrone	NA	0	148, 150	NA
140	10-Hydroxy-10-allylanthrone	HBr gas	10-Bromo-10-(2-bromopropyl)anthrone	NA	0	144	NA
141	10-Isoamylideneanthrone	Br ₂ /CS ₂ or Br ₂ /AcOH	10-Bromo-10-(1-bromoisoamyl) anthrone	NA	+2	148, 150	NA
142	10-Ethyl-9,10-DHA	AcOH/HNO ₃	10-Ethyl-10-nitroanthrone	NA	+2	30, 147	NA

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
143a	10-Phenyl-9-anthronyl acetate or 10-Phenyl-9-anthronyl methyl ether	AcOH/HNO ₃	10-Phenyl-10-nitro-anthrone	NA	+2	151	NA
b	9-anthranyl acetate	AcOH/HNO ₃	10-Nitroanthrone	NA	+2	151	NA
144a	10-Methyl-9-anthranyl methyl ether	AcOH/HNO ₃	10-Methyl-10-nitro-anthrone	NA	+2	152	NA
b	9-Anthranyl alkyl esters	AcOH/HNO ₃	10-Nitroanthrone	NA	+2	152	NA
145	10-Methyl-10-anthracene carbaldehyde oxime	NO ₂ gas (10 equiv)/Ether	10-Methyl-10-nitro-anthrone	27	+2	154	NMR/MS ¹³ C-NMR/IR
146a	10-Phenyl-9-methoxy-anthracene	AcOH/HNO ₃	10-Phenyl-10-nitro-anthrone	50	+2	153	NMR/IR
b	10-Phenyl-9-anthranyl acetate	AcOH/HNO ₃	10-Phenyl-10-nitro-anthrone	20	+2	153	NMR/IR
147	Anthrone	AcOH/HNO ₃	10-Nitroanthrone	80	+2	162	NA
148	Anthracene	Pyridium Nitrate	10-Nitroanthrone	NA	+2	155	NA

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
149a	10-Diazoanthrone (DAAN)	DMF/sulfur/heat	10-Thioanthraquinone	57	0	158	IR/UV
b	10-Thioanthraquinone	CHCl ₃ /2,3-dimethyl butadiene	10-Thioanthraquinone-2,3-dimethyl butadiene adduct	89	-2	158	NMR
c	10-Thioanthraquinone	Cyclopentadiene/CH ₂ Cl ₂	10-Thioanthraquinone cyclopentadiene adduct	90	-2	158	NMR
d	10-Thioanthraquinone	P(OMe) ₃ /CH ₂ Cl ₂	10,10-Anthrone thiirane	60	-2	158	NMR/IR
e	DAAN + 10-Thioanthraquinone	CH ₂ Cl ₂	10,10-Anthrone thiirane	53	-2	158	IR
f	10-Thioanthraquinone	40% Peracetic acid/CHCl ₃	10-Monothioanthraquinone S-oxide	NR	+2	158	IR
150a	Anthrone	DMF (or DMA) pyridine/heat/di-thiobisphthalimide	10-Thioanthraquinone	37.5	+2	156	NMR/IR
b	10-Thioanthraquinone	CHCl ₃ /pyridine 4,4-dimethyl dimedone	10-Dimedone sulfide anthrone	72	-2	156	NMR/IR

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
c	10-Thioanthraquinone	2,3-Dimethyl butadiene	10-Thioanthraquinone-2,3-dimethyl butadiene adduct	69	-2	156	NMR/IR
151	Bianthrylidene	Toluene/sulfur/ $h\nu$	10-Thioanthraquinone	78	+4	165	NA
152	Anthraquinone	HF/H ₂ S	10,10-Dianthrone disulfide	NR	-2	164	IR
153	10-Hydroxy-10-R anthrone	HCl/EtOH	10-Ethoxy-10-R-anthrone	see below	0	163	NA
a	R = C ₆ H ₅	HCl/EtOH	R = C ₆ H ₅	50	0	163	NA
b	R = <i>p</i> -MeO-C ₆ H ₄	HCl/EtOH	R = <i>p</i> -MeO-C ₆ H ₄	50	0	163	NA
c	R = C ₁₀ H ₇	HCl/EtOH	R = C ₁₀ H ₇	50	0	163	NA
154	Anthraquinone	Hydroxylamine	Anthraquinone monooxime	98	0	166	IR
155a	Anthrone	DMF/H ₂ O/HCl/ NaNO ₂	Anthraquinone monooxime	98	+2	167	NMR/MS ¹³ C-NMR/IR
b	Anthraquinone monooxime	THF/LiAlH ₄	Anthraquinone monoimine	97	0	167	NMR/MS ¹³ C-NMR/IR

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
156	Anthraquinone	2,2-Diphenylvinyl magnesium bromide	10-Hydroxy-10- (2,2-diphenylvinyl) anthrone	36	-2	167	IR
157	10-Phenylanthrone	NBS/C ₆ H ₆ /h ν basic aq. workup	10-Hydroxy-10- phenylanthrone	91	-2	168	NMR/ ¹³ C-NMR MS/IR
158	Anthrone	SOCl ₂ /pyridine	10-Chlorosulfinyl anthrone	36	+2	36	IR/NMR
159	Anthraquinone	Methoxybutenyne liq. NH ₃ /acetone/ BuOAc/resin	10-Hydroxy-(4- methoxy-but-3-en-1- yne) anthrone	NR	-2	169	NR (Patent)
160	Anthraquinone	1) EtMgCl 2) HCl	10-Chloro-10-ethyl anthrone	NR	-2	170	NR
161	Anthracene	1) Pb(OAc) ₄ /C ₆ H ₆ 2) Pb(OAc) ₄ /AcOH	10-Acetoxyanthrone	20	+4	142	NA
162a	10-Methylanthrone	EtOH/10% KOH/ 30% H ₂ O ₂	10-Hydroxy-10- methylanthrone	67	+2	67	NA
b	10-Methyl-10- hydroxyanthrone	Acetic anhydride 100° C	10-Methyl-10- acetoxyanthrone	91	0	67	NA

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
163a	Anthrone	<i>p</i> -Tosylazide/EtOH piperidine/RT	10-Diazo- <i>p</i> -tosyl anthrone	94	+4	172	NA
b	10-Diazo- <i>p</i> -tosyl anthrone	AcOH	10-Acetoxyanthrone	94	-2	172	NA
164	10-Methylene anthrone	AcOH/HNO ₃	10-Hydroxy-10- nitromethylanthrone	40	+2	173	NA
165	10-Chloro-10-phenyl- 9-(phenylimine) anthrone	EtOH	10-Ethoxy-10- phenylanthrone	100	0	174	NA
166	9,9-Dimethoxy-10- chloro-10-nitro-DHA	Et ₂ O/Reflux	10-Chloro-10- nitroanthrone	91	0	175	NA
167a	Anthraquinone	BrMg-(CH ₂) ₄ -H (1/2 eq.)	10-Butyl-10- hydroxyanthrone	35	-2	115	NA
b	10-Butyl-10- hydroxyanthrone	Acetic anhydride	10-Acetoxy-10- butylanthrone	NA	0	115	NA
c	10-Butyl-10- hydroxyanthrone	AcOH/H ₂ SO ₄	10-(1-Butenyl)- anthrone	48	-2	115	NA
d	10-(1-Butenyl)- anthrone	Br ₂	10-Bromo-10-(1- bromobutyl) anthrone	97	+2	115	NA

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
167e	Anthraquinone	Isoamyl bromide/ Mg	10-Hydroxy-10- isoamyl anthrone	65 (crude)	-2	115	NA
f	10-Hydroxy-10- isoamylanthrone	Acetic anhydride	10-Acetoxy-10- isoamyl anthrone	NA	0	115	NA
168	10,10-Dibromo- anthrone	H ₂ N-NH-COC ₆ H ₅ / base	Anthraquinone benzoyl hydrazone	NA	0	176	NA
169a	10-Methylene- anthrone	SO ₂ X ₂ (3 equiv)/ CH ₂ Cl ₂ (X = Cl or Br)	10-X-10-(1-X-methyl) anthrone (X = Cl or Br)	X = Cl; 75 X = Br; 86	+2	102	NA
b	10-Benzylidene- anthrone	SO ₂ X ₂ (3 equiv)/ CH ₂ Cl ₂ (X = Cl or Br)	10-X-10-(1-X-benzyl) anthrone (X = Cl or Br)	X = Cl; 75 X = Br; 86	+2	102	NA
170	10-Anisylidene anthrone	Br ₂	10-Bromo-10-(1- bromoanisyl) anthrone	85	+2	90	UV/IR/ NMR/MS
171	DAAN	CCl ₄	10-Chloro-10-(1,1,1- trichloromethyl) anthrone	31	-2	177	NMR/IR
172a	10-Phenyl-10- hydroxyanthrone	1-Octanol/C ₆ H ₆ <i>p</i> -toulenesulfonic acid	10-Phenyl-10-(1-octyl ether) anthrone	95	0	178	NMR

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
172b	10-Phenyl-10-hydroxyanthrone	1-Hexadecanol/C ₆ H ₆ / <i>p</i> -toulenesulfonic acid	10-Phenyl-10-(1-hexadecyl ether) anthrone	88	0	178	NMR/IR
c	10-Phenyl-10-hydroxyanthrone	Cholesterol/C ₆ H ₆ <i>p</i> -toulenesulfonic acid	10-Phenyl-10-(1-cholesteryl ether) anthrone	59	0	178	NMR/IR
d	10-Phenyl-10-hydroxyanthrone	2-Octanol/C ₆ H ₆ <i>p</i> -toulenesulfonic acid	10-Phenyl-10-(2-octyl ether) anthrone	75.5	0	178	NMR/IR
e	10-Phenyl-10-hydroxyanthrone	Cyclohexanol <i>p</i> -toulenesulfonic acid/C ₆ H ₆	10-Phenyl-10-(1-cyclohexyl ether) anthrone	55	0	178	NMR/IR
f	10-Phenyl-10-hydroxyanthrone	1-Dodecyl alcohol <i>p</i> -toulenesulfonic acid/C ₆ H ₆	10-Phenyl-10-(1-dodecyl ether) anthrone	86	0	178	NMR/IR
g	10-Phenyl-10-hydroxyanthrone	EtOH/HCl	10-Phenyl-10-(1-ethyl ether) anthrone	90	0	178	NA
h	10-Phenyl-10-hydroxyanthrone	1,3-Butanediol/ <i>p</i> -toulenesulfonic acid/C ₆ H ₆	10-Phenyl-10-(1-butyl-3-ol ether) anthrone	79	0	178	NMR

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
173a	Anthraquinone	NaC $\equiv$ CC ₆ H ₅	10-Hydroxy-10-(phenyl ethynyl) anthrone	NA	-2	179	NA
b	10-Hydroxy-10-(phenyl ethynyl) anthrone	H ₂ /Pd or Raney Nickel	10-Hydroxy-10-(2-phenyl ethyl) anthrone	NA	0	179	NA
174	10-Cyano-10-R-anthracene R = OCH ₃ or CO ₂ Me	HCl/ether	10-Cyanoanthrone	NA	0	180	NA
175	Anthrone	Triethyl-ortho-formate (10 equiv)/H ⁺ catalyst	10-(1,1-Diethoxy-methyl) anthrone	65	0	181	IR/NMR
176a	10-Benzalanthrone epoxide	BF ₃ /C ₆ H ₆ /ether	10-Formyl-10-phenyl anthrone	47	0	182	IR/NMR
b	10-R ₃ -Substituted-Benzylidene anthrone R ₃ = H, C ₆ H ₅ , C ₆ H ₄ - <i>p</i> -Cl	PO-(OR ₁) ₂ or PO-(OR ₂) ₂ / Xylene reflux R ₁ = Me R ₂ = Et	10-R-anthrone R = (CHR ₃ -PO-(OR ₁) ₂) R = (CHR ₃ -PO-(OR ₂) ₂) (R ₁ = Me; R ₂ = Et R ₃ = H, C ₆ H ₅ , or C ₆ H ₄ - <i>p</i> -Cl)	Above 85	0	182	IR/NMR

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
177	Anthrone	Cl(CH ₂) ₂ COC ₆ H ₅ or CH=CHCOC ₆ H ₅ H ₂ SO ₄ (70%)	10-R or 10,10-Di-R anthrone R = CH ₂ CH ₂ COC ₆ H ₅	NA	0	183	NA
178		AlCl ₃ /C ₆ H ₆		see below	0	184	IR/UV ¹ H-NMR/ ¹³ C-NMR
a	R = Me	AlCl ₃ /C ₆ H ₆	R = Me	52.8	0	184	IR/UV ¹ H-NMR/ ¹³ C-NMR
b	R = Et	AlCl ₃ /C ₆ H ₆	R = Et	49.2	0	184	IR/UV ¹ H-NMR/ ¹³ C-NMR
c	R = <i>n</i> -Propyl	AlCl ₃ /C ₆ H ₆	R = <i>n</i> -Propyl	26.6	0	184	IR/UV ¹ H-NMR/ ¹³ C-NMR
d	R = <i>i</i> -Butyl	AlCl ₃ /C ₆ H ₆	R = <i>i</i> -Butyl	29.6	0	184	IR/UV ¹ H-NMR/ ¹³ C-NMR

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
e	R = Me	TiCl ₄ /C ₆ H ₆	R = Me	73	0	184	IR/UV ¹ H-NMR/ ¹³ C-NMR
179		HCl/EtOH	10-Hydroxy-10-phenyl anthrone and 10-Amino-10-phenyl anthrone	100	0	171	UV

Note: *c*-C₆H₁₁ = cyclohexyl functional group
n-C₆H₁₃ = *n*-hexyl functional group

Application of Reducing Agents To Form 10-Mono- and 10,10-Dialkylated Anthrones

Reducing agents have been employed to form carbon-carbon bonds at the C-10 position of anthrone. Examples of reagents and reaction conditions of this type include Grignard salts¹⁸⁵⁻¹⁹¹ and the sodium salts of alkynes^{179,191} combined with anthraquinone, potassium metal reactions with 1,2-dibenzoyl benzene,^{192,193} and most recently organometallic indium reagents with anthraquinone.¹⁹⁴ Additional substrates employed for these reductions have included phthalide derivatives, 10-methyleneanthrone, and anthrone itself.

One example of a two-electron reducing reaction combined equimolar quantities (60 mmol) of the sodium salts of various substituted alkynes¹⁹¹ and anthraquinone (**1**) in DMF (Scheme 31; entry 189, Table 10). The products, 10-hydroxy-10-alkynylantrones (**57**), were formed in yields greater than eighty-two percent. A single keto group of **1** underwent nucleophilic attack by the alkyne anion; the resulting alkoxide (**57**) was protonated on work up and isolated. Further reaction of the second keto functional group of the alkoxide (**57**) is limited by the use of equimolar quantities of starting reagents and by the introduction of bulky groups at the C-10 position.

While the yields for the alkyne based reactions were high, this was not the

Scheme 31: Formation of 10-Alkynyl-10-Hydroxyanthrone Derivatives¹⁹¹

case when Grignard reagents were used directly with anthrone. A mixture of products has been reported. One complication with the direct combination of anthrone and Grignard reagents has been the abstraction of an acidic C-10 proton (Scheme 32). Formation of intermediates **58** and **59** has been proposed based on final products isolated, **61** and **62**, respectively. Formation of anion **59** can compete as a nucleophile by attack on the keto functional group of **2**, leading to formation of intermediate **60** which upon acidification during the work up undergoes dehydration. Final products **61** and **62** were isolated.

Scheme 32: Side Product Formation from the Direct Application of Grignard Reagents with Anthrone¹⁹¹

The application of organometallic reagents to perform either oxidation or reduction reactions on anthraquinone, anthrone, or substituted derivatives has only recently been published. Recently a single step, two-electron reductive alkylation of anthraquinone with a non-Grignard organometallic reagent¹⁹⁴ was reported; the isolated products were 10-hydroxy-10-allyl-anthrone (**63**) and the 3,3-dimethylallyl derivative (**64**, Scheme 33). **63** was prepared as follows: anthraquinone (2 mmol) was combined with (allyl)₃In₂I₃ (2 mmol) in DMF; the reaction was stirred at 20 °C for 3 hours and the product isolated. **64** was similarly prepared except the reaction time was increased to 20 hours with the 3,3-dimethylallyl indium compound. The yields for **63** and **64** were 100 and 31%, respectively. The significant decrease in yield for the prenyl substituted derivative, **64**, was attributed to an increase in steric bulk of the dimethylallyl alkylating group, in spite of the increased reaction time.

In addition to the formation of 10-hydroxy-10-propargylic anthrone derivatives outlined above (Scheme 31), anthraquinone can also undergo a net 4-electron reduction by employing excess sodium alkyne salt.¹⁹¹ The product, 9,10-dihydroxy-9,10-dipropargylic-9,10-dihydroanthracene, has a net oxidation state of zero. Preparation of these zero oxidation state anthracene derivatives (Scheme 2) has most notably been accomplished through the use of excess Grignard reagents^{201, 202} and sodium carbanion salts¹⁹¹ in the presence

Scheme 33: Reductive Alkylation of Anthraquinone¹⁹⁴

of anthraquinone since this reaction generally occurs at the C-9 and C-10 carbonyl groups to form the diol on work up. The reaction of anthraquinone and two equivalents of tertiary Grignard reagents such as *t*-butyl magnesium chloride result in the formation of 3,10-di-*t*-butyl-10-hydroxyanthrone.¹⁹⁶ The bulky C-10 *t*-butyl group and the alkoxide generated by the initial nucleophilic attack sterically impede a tetrahedral approach to the C-9 carbonyl

group.¹⁹⁶ The reaction is a net 2-electron reduction as defined by this thesis.

Note, due to the common application of Grignard reagents to form diols from anthraquinone, the data in Table 10 regarding the diol formations is intended to be representative of this type of reaction and is not intended to be a comprehensive listing of diol formation in this manner. Reduction of the carbonyl functional group(s) of anthrone derivatives and anthraquinone with standard reducing reagents such as lithium aluminum hydride¹⁹⁷ (10-spirocyclopropyl-anthrone), diborane¹⁹⁸ (10-benzylidene anthrone) and sodium borohydride²⁸ (anthraquinone) to yield an alcohol or diols has also been demonstrated.

Anthraquinone has also been utilized in a series of Diels-Alder reactions that form a C-9/C-10 ethane bridge above the plane of the molecule. The reaction proceeds under base catalyzed reaction conditions in the presence of electron deficient alkenes to form 9,10-dihydroxy-9,10-ethano-9,10-dihydroanthracene derivatives. This is a net four-electron reduction. These compounds undergo carbon-carbon bond cleavage in the presence of strong acids to yield 10-alkyl-anthrone derivatives (entries 205 and 206).^{167,206} The reactive methine carbon of one 10-alkylanthrone derivative was then converted to 10-alkyl-10-hydroxyanthrone in the presence of potassium permanganate. A summary of the reactions is compiled in Table 10.

Table 10: Reducing Reagents to Form C-10 Anthrone Derivatives

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	Entries 180 - 206		
					<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
180	10-Methylene-anthrone	Phenyl magnesium bromide	10-Benzylanthrone	NA	0	99	NA
181	Diphenyl phthalide	1) AlCl ₃ /C ₆ H ₆ 2) H ⁺	10,10-Diphenyl-anthrone	NA	0	185	NA
182	Dimethyl phthalide	1) AlCl ₃ /C ₆ H ₆ 2) H ⁺	10,10-Dimethyl-anthrone	NA	0	186-188	NA
183	Diethyl phthalide	1) AlCl ₃ /C ₆ H ₆ 2) H ⁺	10,10-Diethyl-anthrone	NA	0	185, 187, 188	NA
184	o-Dibenzoyl benzene	Phenyl magnesium bromide	10-Hydroxy-10-phenylanthrone	NA	0	189	NA
185	Anthraquinone	Sodium phenyl acetylide	10-Hydroxy-10-phenylethenyl-anthrone	NA	-2	191	NA
186	Anthraquinone	<i>n</i> -Propyl magnesium bromide/ether	10-Hydroxy-10-(<i>n</i> -propyl)anthrone	20	-2	200	NA

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
187	Anthraquinone	Neopentyl magnesium bromide	10-Hydroxy-10-neopentylanthrone	18.3	-2	199	NR
188	Anthraquinone	Br-CH=C(C ₆ H ₅) ₂ /Mg	10-[2,2-(Diphenyl ethylene)] anthrone	36	-4	167	NR
189a	Anthraquinone	NaC≡CH DMF	10-Hydroxy-10-ethynyl anthrone	89	-2	191	NR
b	Anthraquinone	NaC≡C(CH ₂) ₃ CH ₃ DMF	10-Hydroxy-10-(1-hexyne-1-yl) anthrone	90	-2	191	NR
c	Anthraquinone	NaC≡CC ₆ H ₅ DMF	10-Hydroxy-10-(2-phenyl-(1-ethenyl)) anthrone	83	-2	191	NR
d	Anthraquinone	NaC≡CCl DMF	10-Hydroxy-10-(2-chloro-(1-ethenyl)) anthrone	76	-2	191	NR
e	Anthraquinone	NaC≡CCH ₂ -(NMe ₂) DMF	10-Hydroxy-10-(3,3-dimethyl amino-(1-propyn-1-yl)) anthrone	86	-2	191	NR

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
189f	Anthraquinone	NaC≡CBr/ DMF	10-Hydroxy-10-(2-bromo-(1-ethenyl))-anthrone	83	-2	191	NR
g	10-Hydroxy-10-ethynyl anthrone	KOH/Me ₂ SO ₄	10-Methoxy-10-ethynyl anthrone	93	0	191	NR
h	Anthraquinone	NaC≡CMe DMF	10-Hydroxy-10-propen-1-nyl anthrone	86	-2	191	NR
i	10-Hydroxy-10-propen-1-nyl anthrone	KOH/Me ₂ SO ₄	10-Methoxy-10-propen-1-nyl anthrone	86	0	191	NR
j	10-Hydroxy-10-(1-hexyne-1-yl) anthrone	KOH/Me ₂ SO ₄	10-Methoxy-10-(1-hexyne-1-yl) anthrone	90	0	191	NR
k	10-Hydroxy-10-(2-phenyl-(1-ethenyl)) anthrone	KOH/Me ₂ SO ₄	10-Methoxy-10-(2-phenyl-(1-ethenyl)) anthrone	92	0	191	NR
l	Anthraquinone	NaC≡CH excess/DMF	9,10-Dihydroxy-9,10-ethynyl anthrone	96	-4	143	NA

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
189m	Anthraquinone	$\text{NaC}\equiv\text{CC}_6\text{H}_5$ excess/DMF	9,10-Dihydroxy-9,10-di-(2-phenyl-(1-ethenyl)) anthrone	70	-4	191	NR
n	Anthraquinone	$\text{NaC}\equiv\text{CMe}$ excess/DMF	9,10-Dihydroxy-9,10-di-(2-methyl-(1-ethenyl)) anthrone	90	-4	191	NR
o	Anthraquinone	$\text{NaC}\equiv\text{C-CH}_2\text{-COH}(\text{C}_6\text{H}_5)_2$ / DMF	10-[(4,4-Diphenyl-4-hydroxy-butyn-1-yl]-10-hydroxy anthrone	77	-2	191	NR
190	Anthraquinone	$\text{HC}\equiv\text{C-CH=CH-(OMe)}_1$ /liq. NH_3 acetone/butyl acetate/resin	10-Hydroxy-10-[($\text{C}\equiv\text{C-CH=CH(OMe)}$)] anthrone	NA	-2	193	Patent
191	Anthrone	BrMg-CH=CH_2	10-(9-Anthranyl)-anthrone	20	0	145	NMR
192	1,2-Dibenzoyl benzene	1) Potassium metal/ $\text{Et}_2\text{O}/\text{N}_2$ 2) $\text{MeOH}/\text{H}_2\text{O}$ or 1) Na°	10-Phenyl-10-hydroxyanthrone	49	-2	192	NA
				NR			

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
193a	Anthraquinone	DMF/RT/3 h (Allyl) ₃ In ₂ I ₃	10-Allyl-10-hydroxy-anthrone	100	-2	194	NMR/IR
b	Anthraquinone	DMF/RT/20 h (3,3-Dimethyl-allyl) ₃ In ₂ I ₃	10-(3,3-Dimethyl-allyl)-10-hydroxy-anthrone	31	-2	194	NMR/IR
194	10,10-Diallyl anthrone	Pd on C(5%) /H ₂ ethyl acetate	10,10-Dipropyl anthrone	80.5	0	61	IR
195	Anthrone	Bromo- or chloro-styrene/Mg/THF	9-(<i>p</i> -Vinyl-phenyl)-9-hydroxy-9,10-DHA	25	-2	201	IR
196	Anthraquinone	Phenyl magnesium bromide/excess	9,10-Diphenyl-9,10-dihydroxy-9,10-DHA	NA	-4	202	NA
197	Anthraquinone	1-Naphthyl magnesium bromide/excess	9,10-Dinaphthyl-9,10-dihydroxy-9,10-DHA	NA	-4	203	NA
198	Anthraquinone	Ethyl magnesium bromide/excess	9,10-Ethyl-9,10-dihydroxy-9,10-DHA	36	-4	204	NA
199	10-Phenylanthrone	Phenyl magnesium bromide/excess	9,10-Diphenyl-9-dihydroxy-9,10-DHA	56	-4	205	NA

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
200	10-Spirocyclopropyl anthrone	LiAlH ₄ /ether	10-Spirocyclopropyl-9-hydroxy-9,10-DHA	71	-2	197	NMR
201	10,10-Dibenzyl anthrone	Diborane	10,10-Dibenzyl-9-hydroxy-9,10-DHA	75	-2	198	NA
202	Anthraquinone	NaBH ₄ /MeOH	9,10-Dihydroxy-9,10-DHA	65	-4	28	IR/NMR
203	Anthraquinone	<i>t</i> -Butylmagnesium chloride/ether /excess	3,10-di- <i>t</i> -Butyl-10-hydroxyanthrone	25	-2	196	UV/IR NMR
204	10-Methylene anthrone	N-Methyl maleimide/H ₂ Pd on C(10%) pyridine	10-Methylanthrone	NA	0	167	NA
205	Anthraquinone	N-Methyl maleimide/H ₂ /Pd on C(10%)/pyridine	9,10-Dihydroxy-9,10-N-methyl maleimido-9,10-DHA	95	-4	167	IR, ¹ H-NMR/ ¹³ C-NMR/MS
b	Anthraquinone	trans-1,2-Dicyanoethene/H ₂ /Pd on C(10%)/pyridine	trans-11,12-Dicyano-9,10-ethano-9,10-dihydro-9,10-DHA	94	-4	167	IR, ¹ H-NMR/ ¹³ C-NMR/MS

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
c	Anthraquinone	cis-1,2-Dicyano-ethene/H ₂ /Pd on C(10%)/pyridine	cis-11,12-Dicyano-9,10-ethano-9,10-dihydro-9,10-DHA	98	-4	167	IR, ¹ H-NMR/ ¹³ C-NMR/MS
d	Anthraquinone	Dimethyl fumarate/H ₂ /Pd on C(10%)/pyridine	Dimethyl-9,10-ethano-9,10-dihydro-9,10-DHA-11,12-dicarboxylate	60 or 80 (2 methods)	-4	167	IR, ¹ H-NMR/ ¹³ C-NMR/MS
206a	9-Anthranyl acetate	Acrylic acid/ <i>t</i> -butyl catechol/hydroquinone/145° C	9-Acetoxy-9,10-dihydro-9,10-ethano-9,10-DHA-12-carboxylic acid	65	0	206	NA
b	Product from 206a above	HI/reflux	10-(3-Propionic acid) anthrone	95	0	206	IR
c	Product from 206b above	KMnO ₄ /KOH	10-Hydroxy-10-(3-propionic acid) anthrone	95	+2	206	IR
d	10-Hydroxy-10-(3-propionic acid) anthrone	170° C	10-(3-Propionic acid lactone) anthrone	92.5	0	206	NA

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
e	9-Methoxy-anthracene	Maleic anhydride/ xylene reflux	9-Methoxy-9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylic acid anhydride	92.5	0	206	NA
f	Product from 206e above	HI/reflux	10-(2,3-dicarboxylic acid propyl) anthrone	96	0	206	NA

C-10 Spirocycloanthrone Formation and Related Derivatives Isolated from 10-Diazoanthrone and Photochemical Reactions

Formations of 10,10 cyclic derivatives of anthrone are commonly referred to as spirocycloanthrones; formation of C-10 spirocyclopropyl, spirooxirane, spirothiirane, spirocyclobutyl, spirocyclopentyl, or spirocyclohexyl groups are included in this nomenclature. This class of anthrone derivatives has been of interest to chemists studying the solid and solution conformations of anthrone derivatives and related congested polycyclic molecules. The ring systems including C-10 lie perpendicular to the tricyclic ring system of anthrone. The formation of two spirocycloanthrone⁵⁰ derivatives was reported previously (as a methoxide promoted C-10 dialklation reaction; entries 46 and 47, Table 5). The conformational analysis of this class of anthrone derivatives will be reviewed later in this thesis.

A considerable effort has been devoted to the efficient preparation of C-10 spirocycloanthrones. The formation of this class of compounds has most notably been accomplished by one of the following major synthetic routes: (a) addition of a carbene or ylide across a C-10 exocyclic double bond (C=C, C=O, C=S, C=N) or (b) reaction with 10-diazoanthrone (DAAN, 54, Scheme 34). DAAN itself may react by one of several routes that include: 1,3-dipolar cycloaddition reactions with alkenes or alkynes (the alkyne reaction yields

spiroanthronepyrazole²⁰⁷ (**65**, Scheme 34)) or, more commonly, the carbene of anthrone (**66**) and nitrogen gas after thermal or photolytic decomposition of the diazo functional group. The carbene (**66**) may then react by one of three routes, addition to a carbon heteroatom or carbon carbon pi bond or by insertion into a carbon hydrogen bond²⁰⁸ (**67**, Scheme 34).

Further rearrangement of an initial insertion product may be photochemically induced. This is especially prevalent when heteroatoms are present in small strained ring system and stable products can be formed (**68**, Scheme 35). These rearrangement reactions have been reported with the combination of DAAN and furan²⁰⁸ or thiophene²⁰⁹ to yield the aldehyde (**68A**) or thioaldehyde (**68B**) derivatives (Scheme 35). In addition, ring systems containing pyrazole functional groups can be photochemically or thermally induced to form spirocyclopropene ring systems²⁰⁷ (entry 211 h, Table 11). The driving force for this reaction is the formation of nitrogen gas.

Attempts to repeat the original synthesis of 10-spirocyclopropylanthrone failed;⁷⁹ a successful synthesis required a single equivalent of 10-methyleneanthrone and 10 equivalents of diazomethane in order to achieve 100% conversion to product.⁷⁹ The quantity of diazomethane required limits the scale of the reaction due to the hazardous nature of this reagent. An alternate

synthesis of 10-spirocyclopropylanthrone^{79,80} and 10-spirooxiraneanthrone²¹⁰ has been successfully prepared by employing $(\text{CH}_3)_2\text{S}^+-\text{(CH}_2\text{)}^-$ in DMSO with 10-methyleneanthrone (86% crude yield, 70 g) and anthraquinone (95% crude yield), respectively.

In order to prepare 10-spirocyclopropylanthrone with substitution on the spirocyclopropyl ring, DAAN has been the primary reagent employed in combination with substituted alkenes. Yields vary significantly for these DAAN based reactions but a range of 40 - 60 percent product is not uncommon. The primary advantage of DAAN based synthesis has been access to a class of sterically congested compounds where few alternative routes of preparation have been developed.

Recent reports by Kim et al.^{211,212} have described the formation of a novel C-10 spirocyclobutylether derivative of anthrone (**69**, Scheme 36; Table 11, entry 200). Formation of this unusual product occurred upon exposure of anthraquinone (**1**) to 350 nm light in cyclohexene. The reaction was reversible when C-10 spirocyclobutylether anthrone derivative (**69**) was exposed to 254 nm light (Scheme 36). Diphenyl acetylene and anthraquinone on exposure to 350 nm light also react by a similar mechanism to form a comparable intermediate but cyclic strain and reaction conditions lead to irreversible product

formation. This product is believed to proceed with the formation of a strained 10-spirocyclobutylether anthrone intermediate that rearranges to yield the final product, **70**, in 40% yield (Scheme 37). Further photooxidation of the product, **70**, yields a secondary product in 45% yield (compound not shown in Scheme 37). A summary of DAAN and C-10 spirocycloanthrones formation is located in Table 11.

Scheme 34: Reaction Products From 10-Diazoanthrone

Scheme 35: Formation of Strained Spirocyclo Intermediates from DAAN and Furan or Thiophene^{208,209}

Scheme 36: Reversible 10-Spirocyclobutylether Anthrone Reactions with UV Light²¹¹

Scheme 37: Irreversible Diphenyl Acetylene Reaction with Anthraquinone via a Strained 10-Spirocyclobutylether Anthrone Intermediate

Table 11: Formation of C-10 Spirocycloanthrone Derivatives

Entries: 207 - 231

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
207	10-Methylene-anthrone	Diazomethane (10 equiv)	10-Spirocyclopropyl-anthrone	100	0	79, 81	NA
208	10-Methylene-anthrone	DMSO/NaH to generate dimethyl oxosulfonium methylide	10-Spirocyclopropyl-anthrone	86 (crude)	0	79, 80	NMR IR
209	Anthraquinone	$(Me)_2S^+-CH_2^-$	10-Spiroxirane-anthrone	95	-2	210	NR
210a	10-Bromo-10-(1-bromomethyl)anthrone	Ag_2O/H_2O /acetone	10-Spiroxirane-anthrone	92	0	213	NR
b	10-Bromo-10-(1-bromobenzyl)anthrone	Ag_2O/H_2O /acetone	10-(1-phenyl-spirooxirane)anthrone	70	0	213	NR

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
211	DAAN	substituted alkene 3 equiv C ₆ H ₆ /reflux/2 h		see below	-4	140	NMR/IR
a	DAAN	A, B, C = H D = CN		65	-4	140	NMR/IR
b	DAAN	A, B, C = H D = COCH ₃		61	-4	140	NMR/IR
c	DAAN	A, C = H B = CH ₃ D = COCH ₃		56	-4	140	NMR/IR
d	DAAN	A, C = H B, D = COC ₆ H ₅		91	-4	140	NMR/IR
e	DAAN	Nitrosobenzene		72	-4	207	IR

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
211e	DAAN	<i>p</i> -Quinone 3 equiv/ C_6H_6 /2 h reflux		37	-4	207	NMR/IR
f	DAAN	Benzynes (1.9 equiv)/ C_6H_6 / reflux/2 h		87	-2	207	IR
g	DAAN	$R-C\equiv C-R$ ($R = CO_2CH_3$) 1 equiv/ C_6H_6 /RT/ 5 days		64	-2	207	NMR/IR

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
211h	186, product g (R = CO ₂ CH ₃)	<i>hν</i> /Et ₂ O		47	-2	207	NMR/IR
i	DAAN	P(C ₆ H ₅) ₃ 1.05 equiv	(R = CO ₂ CH ₃)	84	0	207	NMR/IR
212	DAAN	C ₆ H ₆ / <i>hν</i> + 1 equiv		see below	see below	214	NMR/MS
a	DAAN	as above, R = H	as above, R = H	100	-4	214	NMR/MS
b	DAAN	as above, R = CH ₃	as above, R = CH ₃	100	-4	214	NMR/MS

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
212c	DAAN	HOCH(CH ₃) ₂ as solvent/ <i>hν</i>		34	-2	214	NMR/MS
213	DAAN			NR	-4	214 142	NMR/MS IR
a	DAAN	A = C ₆ H ₅ , B, C = H	B, C = H, A = C ₆ H ₅	NR	-4	214	NMR/MS
b	DAAN	A, B = C ₆ H ₅ , C = H	A, B = C ₆ H ₅ , C = H	NR	-4	142 214	IR NMR/MS
c	DAAN	A, C = C ₆ H ₅ , B = H	A, C = C ₆ H ₅ , B = H	NR	-4	142 214	IR NMR/MS
d	DAAN	A, B, C = H	A, B, C = H	39	-4	142 214	IR NMR/MS

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
216b	DAAN	2,6-di- <i>t</i> -butyl quinone methide (1 equiv)		42	-2	218	NR
217a	10,10-Bromoanthrone	H ₂ N-NH ₂ /HgO or Ag ₂ O or H ₂ N-NHSO ₂ C ₇ H ₇ / NaOH		97	0	207	IR
b	10-Hydroxylamine anthrone	NaOH/CINH ₂ / H ₂ O	DAAN	NR	0	207	NA
c	DAAN	Azobis(CO ₂ Et) ₂	10-R-anthrone (R = (=N-N(CO ₂ Et) ₂))	75	0	207	NMR/IR

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
217d	DAAN	9,10-phenanthrene quinone		35	0	207	IR
e	DAAN	C ₆ H ₆ /Cu powder reflux		46	-2	207	IR
218	DAAN	Furan (X=O)/h ν or Thiophene (X=S) h ν		X=O: 50% 44% (cis) 6% (trans) X=S, NR	-4	209	NMR IR NMR IR

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
219	DAAN	2,5-dihydrofuran/ <i>hν</i>	10-[2-(2,5-dihydrofuran)] anthrone	40	-4	208	NMR
220	DAAN	Ethyl ether/ <i>hν</i>	10-[2-(2-ethyl ether)] anthrone	20	-4	219	NMR/IR MS
221a	DAAN	Thiobenzophenone/ Δ H	10,10-Dibenzylidene anthrone	71	-4	209	NMR/IR
b	DAAN	Thiobenzophenone/ <i>hν</i>	10,10-Dibenzylidene anthrone +	30	-4	209	NMR/IR
c	DAAN	Thiobenzophenone/ <i>hν</i>	10-(1,1-Diphenyl spirothiuarane) anthrone	60	-4	209	NMR/IR
222	DAAN	N-Methyl pyrrole/ <i>hν</i>	10-(1,1-Diphenyl- spirothiuarane) anthrone	30	-4	209	NMR/IR
			10-(2-N-Methyl pyrrole) anthrone	NR	-4	209	NMR/IR MS

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
223	10-Azido-10-phenyl anthrone	<i>o</i> -dichlorobenzene 190 °C	10-(N-Phenylimine) anthrone	28	+2	220	MS/IR
224	Anthraquinone	Cyclohexene/ $h\nu = 350\text{ nm}$		NR	-2	231	NMR/IR
225	Anthraquinone	Diphenyl- acetylene/ C_6H_6 / $h\nu = 350\text{ nm}$		40 + (45 photo oxide product)	-4	232	NMR/IR MS

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
226	1a) 10-Methylene anthrone or 1b) 10-Benzylidene anthrone	5 mmol of substrate + 15 mmol of ArN ₃ /90 °C (chromatograph) Ar (see below)	<p>3</p>	see below	+2	139	NMR/IR
a	1a or 1b	Ar = C ₆ H ₅	as above	see below	+2	139	NMR/IR
b	1a or 1b	Ar = 4-MeC ₆ H ₄	as above	see below	+2	139	NMR/IR
c	1a or 1b	Ar = 3-MeC ₆ H ₄	as above	see below	+2	139	NMR/IR
d	1a or 1b	Ar = 2-MeC ₆ H ₄	as above	see below	+2	139	NMR/IR
e	1a or 1b	Ar = 4-MeOC ₆ H ₄	as above	see below	+2	139	NMR/IR
g	1a or 1b	Ar = 3-ClC ₆ H ₄	as above	see below	+2	139	NMR/IR
			<p>5</p>				

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
226h	1a or 1b	Ar = 2-ClMeC ₆ H ₄	as above	see below	+2	139	NMR/IR
i	1a or 1b	Ar = 3-NO ₂ C ₆ H ₄	as above	see below	+2	139	NMR/IR

Note: Highest yielding reactions from 202 series above (overall yield in Parentheses):

5a , 100% (11% overall)
 5b, 100% (16% overall)
 5e, 98% (36% overall)
 3f, 100% (34% overall)

227a	10-Methylene anthrone	Diazomethane	10-(2,3-Diazacyclo- spiropentane) anthrone	NA	-2	197	NMR/ ¹³ C-NMR
b	DAAN	Phenyl acetylene	10-(1-Phenyl cyclo- spiropropene) anthrone	48	-4	197	IR/ NMR/MS
c	DAAN	Methylene cyclopropane	10-(1-spirocyclo- pentylospirocyclo- propane) anthrone	13	-4	197	IR/ NMR/MS

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
228	2.5 mmol Anthraquinone	10 mmol amine 2 mmol HCl/ 260 °C/2 h		see below	-4	222	NMR/IR MS/UV
a	2.5 mmol Anthraquinone	as above	R = R' = H	67	-4	222	NMR/IR MS/UV
b	2.5 mmol Anthraquinone	as above	R = H R' = Me	45	-4	222	NMR/IR MS/UV
c	compound product b above	Ca(OH) ₂ / acetone/Me ₂ SO ₄	R = Me R' = Me	NA	0	222	NMR/IR MS/UV
d	compound product b above (0.26 mmol)	50 mL Toulene/2 ml pyridine/ acetyl chloride	R = Me R' = COMe	NA	0	222	NMR/IR MS/UV
e	compound product b above (0.26 mmol)	50 mL Toulene/2 ml pyridine/ phenyl acetyl chloride	R = Me R' = COCH ₂ C ₆ H ₅	NA	0	222	NMR/IR MS/UV

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
229	10-Methylene anthrone	H ⁺	1,2-Di(10-anthrone) cyclobutane	NA	0	223	IR/MS
230a	DAAN	Cyclohexene	10-(2-cyclohexenyl) anthrone	59	-4	177	IR/NMR
b	DAAN	CCl ₄	10-Chloro-10-trichloromethyl anthrone	31	-4	177	IR/NMR
231	10-Benzylidene anthrone	Triethyl phosphite/heat	(also listed in Table 10)	NA	0	224	NA

Formation of 10-Alkyl and Aryl Anthrones Through Thermal, Radical, Photochemical, and Concerted Reaction Pathways

The synthesis of C-10 anthrone derivatives can be accomplished by a wide variety of methods as already demonstrated. The priority for this section is to analyze radical, carbene, and concerted reaction pathways that are typically photochemically or thermally induced. The common driving force for these reactions is the formation of the more thermodynamically stable anthrone derivative. The C-10 anthrone radical intermediates (Schemes 38, 39, 40, 41) for these reactions are stabilized by resonance with the anthrone oxygen (depicted in Scheme 38 (**72A** and **72B**); Scheme 40 (**75A** and **75B**)).

Formation of C-10 anthrone derivatives may be photochemically induced as with addition of ozone and radical initiators to the C-9/C-10 carbons of a wide variety of anthracene derivatives. UV photolysis of anthracene derivatives in the presence of diatomic oxygen or ozone leads to insertion of the reactive oxygen species across the C-9 and C-10 carbons of the central ring of anthracene.^{136,225, 227-229} These reactions form the peroxide from diatomic oxygen and endotrioxide from ozone; C-10 alkyl substituents were present in the substrate in all cases. One novel synthesis prepared 10-methyl-10-hydroxyanthrone from 9,10-endotrioxide-10-methyl-9-*t*-butyl anthracene²²⁵ and the vanadium reagent, VO(acac)₂ (2 eq.) The organometallic reagent selectively

cleaved two oxygen bonds of the trioxide and *t*-butyl group from the starting material; a yield of 100% was reported.

Thermally induced rearrangements of 10-phenyl-9-anthronyl ethers (**71**) have been reported to afford the 10-phenyl-10-R-anthrone derivatives (**73**, R = alkyl, alkene, alkyne, allene or benzyl). One reported synthesis of the above 10-phenylanthrone derivatives employed refluxing mesitylene (165 °C) to convert 0.1 to 0.25 mmol of substituted 9-anthronyl ethers to product in high yield^{230,231} (Scheme 38). Crossover studies of this reaction combined 9-benzyloxy-10-phenylanthracene and 9-*p*-tolyl-10-*p*-tolylloxy anthracene under identical reaction conditions (as Scheme 38) which provided evidence for an intermolecular rearrangement mechanism. 10-Phenyl-10-*p*-methylbenzyl-anthrone and 10-benzyl-10-tolyl anthrone were present as 26 percent of the product mixture.

The presence of lower than statistical amounts of these crossover products can be accounted for by a partial solvent cage effect. A portion of the radical intermediates formed (**72A** and **72B**, Scheme 38) are trapped by anthracene radical faster than they can diffuse into the bulk solvent. The non-crossover products were 10-benzyl-10-phenyl anthrone and 10-phenyl-10-tolyl anthrone.

Scheme 38: Thermal Rearrangement of 9-Allyloxy-10-Phenylanthracene²³¹

Alkyl Groups

- (a) R = CH₂CH=CH₂
- (b) R = CH₂C(Cl)=CH₂
- (c) R = CH₂Ph
- (d) R = CH₂C≡CH

% Yield Compound 73 (above)

100	
100	
100	
55	R = -CH ₂ C≡CH
+	
45	R = -CH=C=CH ₂

A second novel preparation of C-10 monosubstituted anthrones from anthrone was reported by Oki et al.²³² The application of the radical initiator reagent, azobisisobutylnitrile (AIBN), in a solution of pyridine/piperidine solvent (2/1) and anthrone, yields 10-[2-(2-cyanopropyl)] anthrone. This reaction was performed with three different azo starting materials. Product for-

Scheme 40: Proposed AIBN Reaction Mechanism²³²

A photochemical method of preparing 10,10-diphenylanthrone is the decarbonylation of 3,3-diphenyl indane-1,2-dione upon exposure to UV light. 3,3-diphenyl indane-1,2-dione²³³ sustains the loss of carbon monoxide yielding a ketene intermediate that undergoes intramolecular rearrangement to form the carbon-carbon bond.

Another preparation of 10-phenylanthrone in 95 percent yield was published in 1991.²³⁴ This reaction was based on the S_{RN}1 reaction mechanism. The reactions are performed in a DMSO solvent system containing anthrone, iodobenzene, and excess potassium *t*-butoxide. UV light initially promotes the iodobenzene to an excited state. Anthrone that has been deprotonated by potassium *t*-butoxide then transfers an electron to the excited state iodobenzene. The resulting anthrone radical is stabilized by resonance, **75**. The iodobenzene anion then transfers an electron to an unoccupied iodine molecular orbital. This transfer is followed by homolytic bond cleavage to yield an iodide anion and phenyl radical. The anthrone and phenyl radicals then combine to form a carbon-carbon bond at the C-10 position of anthrone²³⁴ to yield **76** (Scheme 41). Without UV light, this reaction does not proceed. This novel approach to 10-phenylanthrone synthesis employs the resonance properties of both the anthrone enolate anion and anthrone radical intermediates in solution.

Scheme 41: Synthesis of 10-Phenylanthrone via S_{RN}1 Reaction Mechanism

A very different approach to the preparation of 10-phenylanthrone utilized two successive Diels-Alder reactions³⁴ (Scheme 42). The first step was the formation of 1-phenylisobenzofuran (**79**) from 2,4-diphenyloxazole (**77**) and benzyne by a Diels-Alder reaction. An unstable intermediate, **78**, undergoes

a retro Diels-Alder reaction to extrude benzonitrile and intermediate, **79**.

79 reacts in situ with a second equivalent of benzyne in a subsequent Diels-Alder reaction to yield the ether, **80**. Acid catalyzed rearrangement of the bridged product completes the transformation to desired product, **76**, 10-phenylanthrone³⁴ (Scheme 42).

Scheme 42: Preparation of 10-Phenylanthrone via Two Diels-Alder Reactions³⁴

Table 12: Formation of 10- and 10,10 Anthrone Derivatives via Thermal, Radical, Photochemical, and Concerted Reactions
Entries: 232 - 247

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
232	(<i>o</i> -C ₆ H ₅ -C=N-) Isopropyl benzene	oxidizing conditions	10,10-Dimethyl-anthrone	97	NA	235	NMR/MS
233	Anthrone	15.8 mmol substrate + 37 mmol (R-N=N-R) pyridine/piperidine	10-R-anthrone	see below	0	232	NMR
a	Anthrone	(R-N=N-R)	R = -C(Me) ₂ CN	88	0	232	NMR
b	Anthrone	(R-N=N-R)	R = -C(Me) ₂ CO ₂ Me	62	0	232	NMR
c	Anthrone	(R-N=N-R)	R = [1-(1-cyano- <i>c</i> -C ₆ H ₁₀)]	82	0	232	NMR
234	3,3-Diphenyl indane-1,2-dione	C ₆ H ₆ (degassed) UV <i>hν</i> (70 h)	10-Phenylanthrone	70	NA	233	NR
235	1,1,3,3-Tetraphenyl indane-1-one	C ₆ H ₆ /Al ₂ O ₃ (peroxide intermediate)	10,10-Diphenyl-anthrone	NR	NA	237	NR

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
236	10-Phenyl-9-R-anthranol 0.1 to 0.25 mmol	substrate/165 °C reflux (mesitylene)	10-Phenyl-10-R-anthrone	see below	0	230, 231	NMR/ IR
a	R = CH ₂ -CH=CH ₂	mesitylene/reflux	R = CH ₂ -CH=CH ₂	100	0	230, 231	NMR/ IR
b	R = CH ₂ -C(Cl)=CH ₂	mesitylene/reflux	R = CH ₂ -C(Cl)=CH ₂	100	0	230, 231	NMR/ IR
c	R = CH ₂ -C ₆ H ₅	mesitylene/reflux	R = CH ₂ -C ₆ H ₅	100	0	230, 231	NMR/ IR
d	R = CH ₂ -C≡CH	mesitylene/reflux	R = CH ₂ -C≡CH + R = CH=C=CH ₂	55 45	0	230, 231	NMR/ IR
237	Anthraquinone	UV/H ₂ SO ₄ (96%)	10-R-anthrone R = H or OH	NR, mixture	-4/-2	237	NR
238	Anthraquinone	UV <i>hν</i> /N ₂ /MeCN + 5 mmol/H ₂ O	10-Hydroxy-10-(hydroxymethyl) anthrone	80	-2	238	NR

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
239		1) 0.1 g. substrate $\text{O}_3/\text{O}_2/\text{MeOH}/$ $-78\text{ }^\circ\text{C}$ 2) TLC isolation		NR	+2	225	NMR
a	$\text{R}_1 = \text{R}_2 = \text{Me}$	as above	$\text{R}_1 = \text{R}_2 = \text{Me}$	NR	+2	225	NMR
b	$\text{R}_1 = \text{Et}, \text{R}_2 = \text{Me}$	as above	$\text{R}_1 = \text{Et}, \text{R}_2 = \text{Me}$	NR	+2	225	NMR
c	$\text{R}_1 = \text{iPr}, \text{R}_2 = \text{Me}$	as above	$\text{R}_1 = \text{iPr}, \text{R}_2 = \text{Me}$	NR	+2	225	NMR
d	$\text{R}_1 = \text{Bn}, \text{R}_2 = \text{Me}$	as above	$\text{R}_1 = \text{Bn}, \text{R}_2 = \text{Me}$	NR	+2	225	NMR
e	$\text{R}_1 = \text{Me}, \text{R}_2 = \text{H}$	as above	$\text{R}_1 = \text{Me}, \text{R}_2 = \text{H}$	NR	+2	225	NMR
f	$\text{R}_1 = \text{Me}, \text{R}_2 = -\text{OMe}$	as above	$\text{R}_1 = \text{Me}, \text{R}_2 = -\text{OMe}$	NR	+2	225	NMR
g	$\text{R}_1 = \text{Me}, \text{R}_2 = -\text{C}_6\text{H}_5$	as above	$\text{R}_1 = \text{Me}, \text{R}_2 = -\text{C}_6\text{H}_5$	NR	+2	225	NMR

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
240	1) 9- <i>t</i> -Butyl-10-methyl anthracene (9,10-Trioxo-9- <i>t</i> -butyl-10-methyl -anthracene) intermediate	1) O ₃ 2) 2+ equiv VO(Acac) ₂ / CH ₂ Cl ₂ /reflux	10-Hydroxy-10-methylanthrone	100	+4	227	NA
241	9-R-10-(N,N,-dimethylamine)anthracene R = OMe, C ₆ H ₅	1) O ₂ /UV <i>hν</i> -70 °C/Et ₂ O 2) HCl/-30 °C 3) HN(C ₂ H ₅) ₂ stir 3h/Et ₂ O	10-Hydroxy-10-R-anthrone R = OMe, C ₆ H ₅	90	+2	227	NMR
242	10-R-9-Anthranol	1) O ₂ bubbling 2 hr. 2) peroxide/EtOH/ H ₂ /PtO ₂	10-Hydroxy-10-R-anthrone	see below	+2	229	NMR
a	R = Et	as above	R = Et	100	+2	229	NMR
b	R = C ₆ H ₅	as above	R = C ₆ H ₅	90	+2	229	NMR
c	R = Me	as above	R = Me	55	+2	229	NMR

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
243	Anthrone	Potassium <i>t</i> -butoxide/PhI 1.03 mmol/ DMSO/ <i>hν</i>	10-Phenylanthrone	95	0	234	NMR/ MS
244	10-Phenylanthrone	10-Phenyl-9-R- anthranol ether with base	10-Phenyl-10-R- anthrone	NR	0	239	NR
a	10-Phenylanthrone	base	R = Allyl	NR	0	239	NR
b	10-Phenylanthrone	base	R = 2,4-pentadiene	NR	0	239	NR
c	10-Phenylanthrone	base	R = -CH ₂ COCH ₃	NR	0	239	NR
245	10-X-9-Nitro- anthracene X = Cl, NO ₂	1) <i>hν</i> conversion (9-nitro conver- sion to nitroso)	10-X-10-Nitroso- anthrone X = Cl, NO ₂	Low, NR	0	240	IR/MS
246		1) <i>hν</i> , H ₂ O/H ⁺ (loss of N ₂)	10-Methyl-10-(2- aminophenyl) anthrone	67	0	226	IR NMR

<u>Entry</u>	<u>Substrate</u>	<u>Conditions</u>	<u>Product</u>	<u>Yield(%)</u>	<u>ΔFGF</u>	<u>Ref.</u>	<u>Spectra</u>
247	2,4-Diphenyloxazole (1-Phenylisobenzofuran intermediate)	2 equiv of Benzzyne	10-Phenylanthrone	26	NA	34	NMR/MS

Anthrone: Keto/Enol Tautomerization

The keto/enol tautomerization of anthrone has long been an area of interest for chemists (Scheme 43, 44). Initially, anthrone and 9-anthranol were believed to be two separate compounds. This belief was maintained until a greater understanding of keto/enol tautomerization had emerged. In 1911, K. Meyer observed that the enol form of anthrone, 9-anthranol (81), slowly isomerized to anthrone in organic solvents.¹⁴ At equilibrium, approximately 11% of 9-anthranol¹⁴ was detected in a solution of ethanol, the balance remaining in the keto, anthrone, form. 9-Anthranol was first prepared by dissolving anthrone in 5 - 10% boiling aqueous sodium hydroxide, the solution was rapidly cooled to -5 °C, followed by the addition of a five percent solution of sulfuric acid to the cooled basic homogenous mixture above. The product, 9-anthranol,¹⁴ was then isolated. One early analytical method for detecting 9-anthranol employed iodine titration,²⁴¹ a system that does not react with anthrone in the absence of acid or base conditions.

Nukada and Bansho²⁴² reported the first optimized synthesis of 9-anthranol. By performing the deprotonation and subsequent acidification reactions under an inert atmosphere of N₂ gas, using thoroughly degassed solvents, and maintaining temperatures as close to -5 °C as possible, minimal impurities

Scheme 43: Anthrone Keto/Enol Equilibrium Constants in Polar and Nonpolar Solvent Systems²⁴⁸

Polar Solvents

	<u>K_e</u>
DMSO	1.6 ± 1
Dimethylformamide	1.3 ± 0.1
Dimethylacetamide	1.8 ± 0.5
Triethylamine	1.1 ± 0.5
Pyridine	1.4 ± 0.5

The equilibrium lies to the right in polar or basic solvents

Nonpolar Solvents

	<u>K_e</u>
Methylene chloride	<0.001
Diethyl ether	0.06 ± 0.02
Benzene	0.0025 ± 0.0005
Ethyl acetate	0.06 ± 0.01

The equilibrium lies strongly to the left in non-polar solvent systems. (Determined UV spectroscopy)

Scheme 44: Keto/Enol Tautomerization of Anthrone Observed in Nonpolar Solvents²⁴⁸ (A) and the Vapor Phase²⁴⁹ (B)

A

B

The equilibrium constant, K_t or K_t' , is defined as: $[\text{Enol}]/[\text{Keto}]$

were formed. This material was used to measure the dipole moment of the product in solution. Kinetic studies by the same authors found the tautomerization reaction to be first order in both polar (MeOH, EtOH)²⁴³ and nonpolar solvents (benzene, toluene).²⁴³ The activation energies in benzene and toluene were reported as 5.8 and 12.4 kcal/mol (iodometric titration), and 4.8 and

12.2 kcal/mol (dielectric analysis) respectively. These relatively low activation energies indicate that small energy barriers to tautomerization exist in the solvent systems studied. Supporting evidence for the first order reaction was provided by means of fluorescence spectroscopy.²⁴⁴

The precise reason(s) the keto form, anthrone, is favored over the enol form, 9-anthranol, has been debated extensively. Only within the past ten years, has the importance of solvent hydrogen bonding and its affect on keto to enol tautomerization been established. In nonpolar deaerated solvent systems, the equilibrium lies exclusively towards the keto form.²⁴⁵ Baba and Takamura's detailed studies of the equilibrium determined anthrone to be more stable by 3.3 and 2.6 kcal/mol in benzene and toluene,²⁴⁵ respectively. The presence of basic solvent systems or weak bases assists in the transfer of a proton from the C-10 carbon to the oxygen of anthrone,^{245,246,247} thus forming 9-anthranol. The presence of the weak base such as triethylamine in a non-polar solvent system stabilized 9-anthranol by hydrogen bonding^{248,249} by 5.2 kcal/mol over anthrone.^{245,246} The autooxidation of 9-anthranol to anthraquinone has also been studied in basic, buffered aqueous dioxan solution.²⁵⁰ According to Beak, et al.²⁴⁸ "the equilibria appear to be controlled almost completely by the hydrogen bonding basicity of the solvent." Many solvents with a wide range of polarities were employed to investigate this effect

(Schemes 43, 44). The anthrone/9-anthranol equilibrium constant was reported to be difficult to accurately measure due to sensitivity to oxidation and slow equilibrium rates in nonpolar solvent systems.²⁴⁸ The keto form of anthrone is the only observed tautomer in the vapor phase²⁴⁹ (Scheme 44).

A second form of keto/enol tautomerization of anthrone has been observed as anthrone can undergo flash photoinduced isomerization reactions^{10,251-253} to yield 9-anthranol (Scheme 45 and 46). Reaction yields significantly increase in solvent systems that readily permit hydrogen atom abstraction such as ether or ethanol. The resulting solvent radicals are stabilized through resonance with oxygen by formation of a radical at the α -carbon atom.

By UV absorption, a single intermediate was observed for the flash photoinduced isomerization reaction. This intermediate has an absorption at 340 nm and was believed to be a ketyl radical (82, Scheme 46). Solvent systems for these reactions required thorough degassing as oxygen, a triplet state quencher, suppresses the radical reactions.²⁵² Additional products were recovered that support a radical based reaction mechanism²⁵³ including bianthranol, disproportionation products, and dimerized solvent molecules (Scheme 47, processes A, B, and C, respectively). In a related preparation, ketyl radicals could be generated in a 2 laser system in which 10,10-dibenzyl-

anthrone underwent benzyl radical cleavage at the C-10 position. Subsequent formation of 10-benzyl-9-anthranol was observed in nonpolar solvent systems.¹⁰ The intermediate radical was undoubtedly stabilized by resonance as similar Schemes 38 and 40, resonance structures **72A/B** and **75A/B**.

Scheme 45: Flash Photolysis Photoisomerization of Anthrone to 9-Anthranol^{252,253}

<u>Solvent</u>	<u>% Yield</u>
Ethanol	high
Ether	~40
<i>n</i> -Heptane	< 3
Acetonitrile	< 3

Note: In the UV spectra, a decrease in the 300 nm absorbance peak of anthrone was followed by an increase and then a decrease of a 340 nm peak. The final absorption peak at 370 nm of the product, 9-anthranol, was then observed.

The 340 nm absorbance peak arises from the proposed ketyl radical intermediate (**82**, Scheme 46).

**Scheme 46: Anthrone Photoisomerization/Flash Photolysis
Reaction Mechanism²⁵³**

The process proceeds through a $n \rightarrow \pi^*$ triplet state.
Exposure to diatomic oxygen, a triplet state quencher,
reportly did not yield 9-anthranol or any other product.

Scheme 46: Continued

Scheme 47: Flash Photolysis/Photoisomerization Formation of Side Products^{252,253}

The proposed radical mechanism is supported by the isolated products and the observation of the reaction in solvents that are hydrogen atom donors. Supporting the formation of the intermediate ketyl radical.

Through long and deliberate research, a greater understanding of the process of keto/enol tautomerization has been achieved as two methods to induce tautomerization have been discovered. The total resonance stabilization energy of the keto (two benzene rings) and enol (one anthracene ring system) forms of anthrone and its effect on the equilibrium has long been debated. The solvent system plays a critical function in the formation of the 9-anthranol as tautomerization is a function of solvent basicity. From Peter Beak's^{248,249} work (Scheme 43; Polar Solvents), the equilibrium constants reveal that complete conversion of anthrone to 9-anthranol does not occur, even in the best solvent system listed, (maximum conversion, DMSO, 72%, Scheme 43). Resonance stabilization energy of anthrone is a few kilocalories per mole greater than 9-anthranol, that is sufficient energy to favor complete anthrone formation in nonpolar solvents. Only with basic solvent systems such as the 5 - 10% boiling aqueous sodium hydroxide solution and subsequent kinetic acidification can pure 9-anthranol be isolated. 9-Anthranol, in the solid state, then slowly isomerizes to the more stable ketone tautomer.¹⁴

Molecular Structure and Spectroscopy of Anthrone and Its C-10 Substituted Derivatives

While the great majority of anthrone research has dealt primarily with the synthetic aspects of anthrone chemistry, a small but significant portion of published papers have addressed the conformational and spectral properties of this class of compounds. Some surprising conformational properties have been established. After years of debate, anthrone itself has only recently been established to exist as a planar molecule.¹²

The primary tools of spectroscopic analysis have been proton NMR and x-ray crystallography in the liquid and solid phases, respectively. These tools as well as other forms of spectroscopy have been used to resolve the poorly understood conformations of anthrones. Another important tool extensively used to predict the conformation(s) of anthrone has been molecular modeling.^{12,254} After years of substantial debate, the conformation of anthrone was firmly determined by Rabideau in 1991.^{12,140} Rabideau's work combined powerful molecular modeling programs, x-ray crystallography, proton NMR and novel synthetic preparations of sterically congested anthrones (reported previously in this thesis; entry 128 a - k, Table 9).

One might expect the conformation of anthrone to be an intermediate

between planar anthraquinone²²⁵ and folded boat-like 9,10-dihydroanthracene. The conformation of anthrone can not be established by x-ray crystallography as the "large, independent out of plane vibration of oxygen in the solid state has precluded determination of whether anthrone is planar or folded along the C-9/C-10 axis of the central ring in the crystal state."^{12,256} In the past, experimental spectral data has resulted in different conclusions regarding the conformation of anthrone in the solid and solution phases. Proton NMR suggests a slowly inverting nonplanar molecule in solution based on interpretation of long range spin-spin coupling constants.²⁵⁷ Dipole moment and Kerr constant data suggest a planar molecule.²⁵⁸ Computational analyses by ab initio, STO-3G MO, 4-31G MO, and MM2 calculations indicate a planar conformation of anthrone with a shallow energy minimum^{12,254} (Scheme 48).

The x-ray crystallographic studies by Rabideau et al.¹² on C-10 substituted anthrone derivatives in conjunction with MM2 calculations for anthrone and its C-10 derivatives (some of the derivatives have no published method of synthesis) determined that as the size of the substituent increased, the degree of folding along the C-9/C-10 axis of the central ring of anthrone also increased. Some discrepancies were noted as the 10-Me- and 10-phenyl-anthrone displayed a smaller degree of folding in the crystal state than was

computationally calculated; this result was attributed to crystal packing forces.¹⁰

Scheme 42: Planar Conformation of Anthrone

The molecular structure cannot be directly determined by x-ray crystallography due to a large out of plane vibration by oxygen. Substantial evidence has been collected that indicates the tricyclic ring system is relatively planar.

Planar structure is supported by:

Ab Initio calculations, STO-3G MO, 4-31G MO, MM2 calculations, Dipole moment calculations, and Kerr constant measurements

Of the following substituents R = H, F, Cl, Br, Me, Et, *i*-Pr, *t*-Bu, Ph, CF₃, and SiMe₃, a preference for pseudoaxial orientation was displayed by all C-10 monosubstituted anthrones except for 10-fluoroanthrone.¹² This observed and computational pseudoaxial preference is a consequence of nonbonding repulsive interaction (van der Waal radii overlap) of the substituent at the C-10 carbon with the C-4/C-5 peri hydrogens.¹² Furthermore, the methyl group of 10-ethylanthrone is preferentially located anti to the methine hydrogen of the C-10 carbon of anthrone, the lowest energy configuration

(Scheme 49). The pseudoequatorial preference of 10-fluoroanthrone was attributed to van der Waal attractive forces between the fluorine substituent and the C-4/C-5 peri hydrogens.¹² An alternative explanation for the pseudoequatorial conformational preference can be attributed to a balancing of the dipole moment forces of the C-10 fluorine group and the C-9 carbonyl group of this proposed anthrone derivative.²⁵⁹ Note, a synthesis of 10-fluoro-anthrone has yet to be published. The C-10 anthrone derivatives of Rabideau's study were determined to exist in the boat or pseudoboat conformations¹² (Scheme 50).

The x-ray crystal structure of 10-spirocyclopropylanthrone has revealed a planar structure, thus minimizing steric interactions between the spirocyclopropyl methylene groups and the C-4/C-5 peri hydrogens.²⁵⁵ AM1 computational calculations for the C-10 spirocyclooxirane analogue indicate a 4.25 kcal/mol energy difference favoring a pseudoaxial methylene group over a pseudoequatorial methylene group. Steric repulsive interactions of the lone electron pairs of oxygen are apparently less than those of the methylene hydrogens in the pseudoequatorial position.²⁵⁵ Other planar derivatives of anthrone, as determined by x-ray crystallography include: anthralin [(1,8-dihydroxy)anthrone],²⁶⁰ 10-[4'-(acetoxyl)phenyl]-10-hydroxyanthrone,^{261,262} and 10,10-divanillylanthrone.²⁶⁴ In each case, different factors may account

for the planar structures of the anthrone derivatives.

Scheme 49: Conformational Preferences of 10-Ethylanthrone and 10-Isopropylanthrone¹²

Note: Both of the above anthrone derivative have the methyl group of the C-10 ethyl substituents anti to anthrone's C-10 methine hydrogen.

Scheme 50: Structural Conformation of C-10 Anthrone Derivatives¹²

pseudoequatorial group

pseudoaxial group

Boat conformations

Pseudoequatorial Groups

R = F

Stabilized by van der Waals attractive forces and dipole moment force.

Pseudoaxial Groups

R = Cl, Br, Me, Et, *i*-Pr, *t*-Bu, Ph, CF₃, SiMe₃

As steric bulk of the above groups increases, ring folding increases to minimize C-4/C-5 peri hydrogen and C-10 substituent steric interactions.

NMR studies of 10-(4-(acetoxy)phenyl)-10-hydroxyanthrone,²⁶¹ 10,10-divanillyl anthrone,²⁶² and a number of related compounds have been determined to exist with the 10-benzyl substituent(s) over the tricyclic ring structure of anthrone²⁶¹ (Scheme 51). In addition, a significant upfield shift in the phenyl protons from the expected 6.6 to 7.0 ppm to 5.3 to 6.6 ppm region was observed by ¹H-NMR. This can be explained by the shielding of the magnetic field by the anthrone ring. The shielding and upfield shifts¹⁸ were also observed in the ¹³C-NMR for the phenyl ring and substituents of that ring system. The ¹H-NMR shielding effect was also observed by Desphande¹⁹ for the allyl substituents of both 10-allyl-10-hydroxyanthrone and 10-(3,3-dimethylallyl)-10-hydroxyanthrone (Scheme 51). The observed NMR shift can be explained by a conformation in which the allyl group, as in the benzyl derivatives described above, lies over the plane of the anthrone ring system.

Evidence supporting this conformational proposal includes a single UV absorbance at 272-288 nm ($\epsilon = 12,000$ -13,000) as opposed to the 2 expected absorbance at 270-280 nm ($\epsilon = 1500$) and 257 nm ($\epsilon = 25,000$). This is indicative of a charge transfer complex²⁶¹ due to π - π stacking of aromatic ring systems.

Lastly, an x-ray crystal structure analysis of 10,10-divanillylanthrone con-

firmed the planar conformation of the tricyclic anthrone ring system in the solid state. The anthrone ring system is sandwiched both above and below by the two substituted benzyl rings²⁶⁴ (similar to the top structure in Scheme 51). The application of spectroscopy to analyze the structure of anthrone has revealed some surprising conformational preferences. The most commonly used method is the examination of the chemical shifts in the ¹H- and ¹³C-NMR spectra. In addition, a limited number of articles have been published based on the analysis of ¹H- and ¹³C-coupling constants of anthrone and its derivatives.

X-ray crystallography is unambiguous but is less commonly employed and of course, does not directly address the issues of solution conformation and conformational mobility.^{5,12,269,263,265-8} The central ring of these C-10 anthrone derivatives can exist in planar or boat conformations. In addition, a calculation of the molecular orientation disorder of anthrone has been published by Reynolds.²⁶⁹

The UV analysis of anthrone has been used to determine rates of keto/enol tautomerization.²⁴⁸ Only a single paper has been devoted exclusively to the mass spectral analysis and fragmentation pathways of anthrone and its 10,10-dideuterated analogue.²⁷⁰

Several additional papers have been published in which anthrone is typically not the primary subject of the research. This research describes data such as ^{13}C -NMR coupling constants of anthracene and anthrone,²⁷¹ the ^{18}O -induced isotope shifts in the ^{13}C -NMR spectra of related anthracene derivatives,²⁷² and the shielding of the C-4 hydrogen of anthraquinone.²⁷³ The final paper describes the IR, UV, and ^{13}C chemical shifts for a wide variety of anthrone derivatives including those with substitution on the C-1 to C-8 ring carbons.²⁷⁴

The major factor that has prevented synthesis of sterically congested 10,10-disubstituted anthrone derivatives is steric interactions with the C-4/C-5 peri hydrogens. Rabideau's x-ray crystallographic studies indicate a direct correlation between substituent size and folding along the C-9/C-10 axis.¹² The larger C-10 functional group will occupy the psuedoaxial position, above the plane of the tricyclic ring system. The smaller C-10 substituent must be located in the psuedoequatorial position, relatively close to the to the C-4/C-5 peri hydrogens. As the size of the second alkylating group increases, the reactivity of the anion decreases. Attempts to prepare 10,10-dicyclohexylanthrone have failed with the same methodology that successfully produced 10-cyclohexyl-10-methyl- and 10-cyclohexyl-10-hexylanthrone.¹²

Scheme 51: Unusual Conformational Structures of Some C-10 Anthrone Derivatives

Significant upfield shift in the ^1H and ^{13}C -NMR for the benzyl group, substituted aromatic benzyl rings, and allyl groups. Strongly indicate the ring is in the shielding region of the anthrone ring during ^1H -NMR and ^{13}C -NMR irradiation.

Aryl ^1H -NMR shift: 5.3 - 6.6 ppm vs. 6.6 - 7.0 ppm (expected)

Additional Evidence:

A single UV peak, indicative of charge transfer complex at 272 - 282 nm vs. expected 2 peaks at 257 and 270 - 280 nm.

X-ray crystallography, supports a structure suggested by NMR analysis

Non-equivalent Me proton NMR signals at 0.79 and 1.34 ppm due to the different electronic environments.

Summary

Over the past one hundred and twenty-one years, significant preparative effort has been directed towards the synthesis of anthrone and its C-10 mono- and disubstituted derivatives. Chemists such as Barnett, Rigaudy, Rosenfeld are but a few that have dedicated their professional lives towards the greater understanding of anthrone preparation and derivatization. Prior to 1958, the preparative work of this class of C-10 substituted compounds was restricted to potassium hydroxide deprotonation/alkylation, Friedel-Craft arylation, and intramolecular cyclodehydration reactions. These types of reactions were limited by yield, purity, and incorporation of non-equivalent C-10 functional groups.

As a greater understanding of solvent, counterion, and resonance (both anion and radical) effects became widely understood, corresponding improvements in synthetic procedures evolved. Utilization of firmly established chemistry, such as Diels-Alder reactions were also applied to the preparation of C-10 monosubstituted anthrone derivatives²⁰⁶ beginning in 1963. Improvements in the selectivity, regiospecificity, and diversity of products were some of the major benefits of this research. Finally, the works of Dalpozza,¹⁴⁰

Chattopahyay,^{51,52} and Rabideau¹⁴³ have made it possible to functionalize the C-10 carbon with a wide variety of non-equivalent functional groups. The size of these substituents can be varied significantly.

Anthrone and anthraquinone derivatives will undoubtedly continue to play a significant role in organic chemistry as intensive research into the biological activity of these compounds will in turn present new challenges to the organic bench chemist. Work in the near future will focus on the 1,8-dihydroxylated anthrone derivatives, commonly found as natural components of plants, such as aloe. Functionalization of the C-10 carbon to increase either hydrophobicity or hydrophilicity can be achieved by numerous methods outlined in this review. Rabideau's work on the conformation of C-10 mono- and disubstituted anthrone derivatives will also benefit pharmaceutical research. The relationship between three dimensional structure of drugs and drug efficacy is now considered an element of rational drug design.

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