REACTIONS OF SOME NON-ENOLISABLE CHLOROKETONES WITH AMIDE ION AND A NEW SYNTHESIS OF ACRIDONES

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B R O C K U N I V E R S I T Y

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ABSTRACT

This research was directed mainly towards the investigation of the reactions of substituted chlorobenzophenones under strongly basic conditions. The work can be divided into two main sections.

The Introduction deals mainly with historical studies on aryne chemistry and the Haller-Bauer reaction.

Section 1 is concerned with syntheses of 2-benzamido-2'-chlorobenzophenone and 2-benzamido-3'-chlorobenzophenone, and with their respective reactions with potassium amide in ammonia. o-Chlorophenylacetic acid was converted to the acid chloride and then by Friedel-Crafts reaction with benzene to ω-(o-chlorophenyl)acetophenone. Reaction with phenylhydrazine and Fischer cyclization gave 3-(o-chlorophenyl)-2-phenylindole, which was ozonized to 2-benzamido-2'-chlorobenzophenone. The isomeric 3'-chloroketone was similarly synthesised from m-chlorophenylacetic acid. Both the 2'- and 3'-chloroketones gave N-benzoylacridone on treatment with potassium amide in ammonia; an aryne mechanism is involved for the 3'-chloroketone but aryne and nucleophilic substitution mechanisms are possible for the 2'-chloroketone.

Hydrolysis of the 2'- and 3'-chloroketones gave 2-amino-2'-chlorobenzophenone and 2-amino-3'-chlorobenzophenone respectively. A second new acridone synthesis is given in the Appendix involving reactions of these two ketones with potassium t-butoxide in t-butylbenzene.

Section 2 deals with the investigation of the reaction of some tricyclic chlorobenzophenones with potassium amide in liquid ammonia. These were 1-chlorofluorenone, which was prepared in several steps from fluoranthene, and 1- and 2-chloroanthraquinones. 1-Chlorofluorenone gave 1-aminofluorenone ; 1-chloroanthraquinone gave 1- and 2-aminoanthraquinones; 2-chloroanthraquinone was largely recovered from the attempted reaction.

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To my parents

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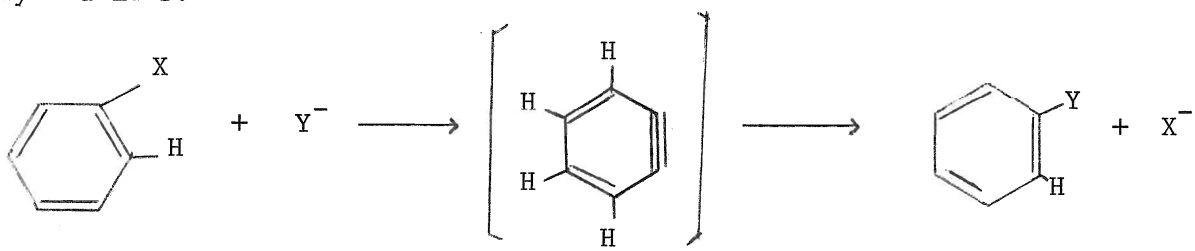
INTRODUCTION

The research described in this thesis deals with the behaviour of various compounds related to the chlorobenzophenones when treated with potassium amide in ammonia. One part of the research is concerned with new syntheses of the acridone system and a second with preparation of 1-aminofluorenone and the two aminoanthraquinones. Aspects of aryne chemistry and of the Haller-Bauer scission reaction which relate to this research are discussed in the Introduction. The Introduction concludes with a note on some better-known routes to acridones and related heterocycles so as to provide the rationale for examining the routes explored in this thesis.

(i) ASPECTS OF ARYNE (BENZYNE) CHEMISTRY

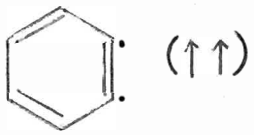
Arynes, e.g. benzyne (I), are frequently generated by treatment with a strong base, such as potassium amide in ammonia, of an unactivated aryl halide. The aryne formed reacts further by adding a nucleophile. The overall result is substitution by an elimination-addition mechanism and is distinct from nucleophilic substitution reactions of activated aryl halides.



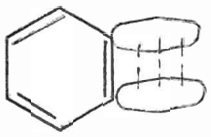
(I)

+ HY

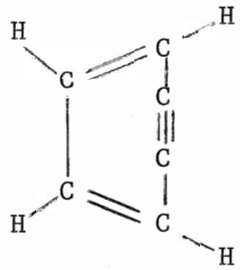
Historically, aryne intermediates were proposed by Stoermer and Kaheref[1] in 1902. However, Wittig[2] was the first to advance the aryne hypothesis with cogent experimental support when in 1942 he specifically rejected the symmetrical formula (I). Three formula types suggested for benzyne are (II), (III), and (IV).



(II)



(III)



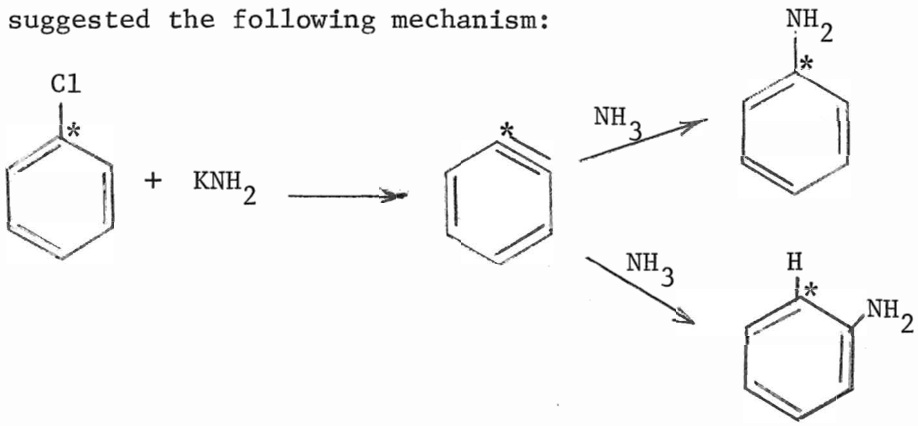
(IV)

Formula (II) shows a diradical;

Formula (III) shows a special kind of triple bond between two sp^2 hybridized carbon atoms;

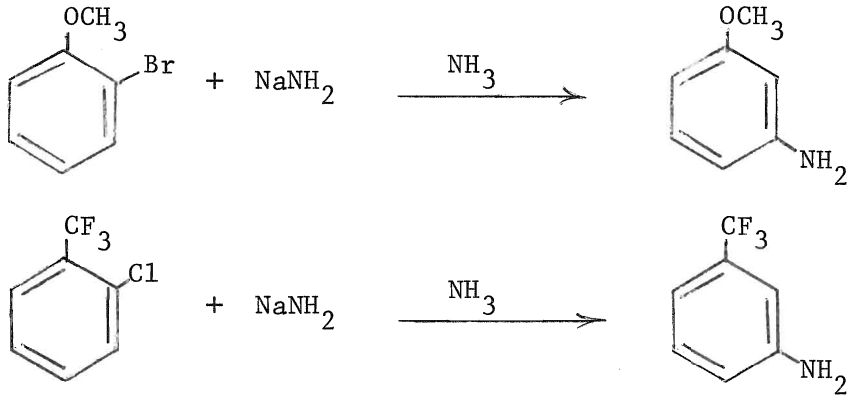
Formula (IV) has the same kind of triple bond as in an acetylene, involving sp hybridization of the two carbon atoms concerned.

Roberts and coworkers[3], in 1953, published experiments which put the aryne hypothesis on the road to general acceptance. They showed that the aryl halides (except fluorobenzene) react with potassium amide in liquid ammonia to form aniline. They further showed that chlorobenzene-1-^{14}C gives nearly equal amounts of aniline-1-^{14}C and aniline-2-^{14}C, and suggested the following mechanism:

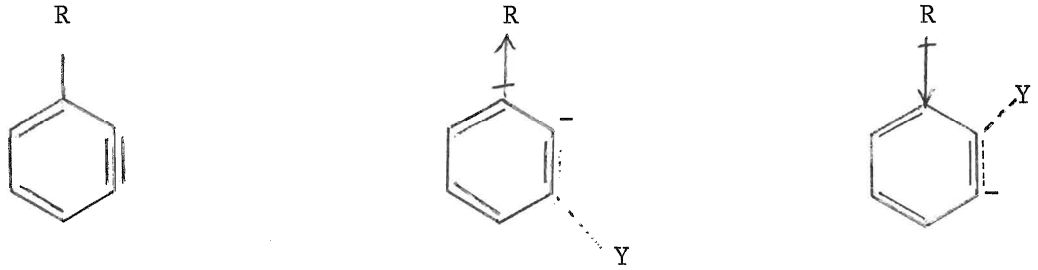


The slight difference from a 1:1 product ratio was of the magnitude and direction expected of a $^{12}C/^{14}C$ isotope effect. From this result, Roberts deduced that benzyne is symmetrical and he favoured formula (III) as the best representation in orbital symbolism. This formula is in agreement with all observed facts, and accommodates the benzyne geometry and resonance stabilization.

In 1936, Bergstrom and Gilman[4] had reported that certain ortho-substituted aryl halides give meta products when treated with sodium amide in ammonia, but they did not offer an explanation.



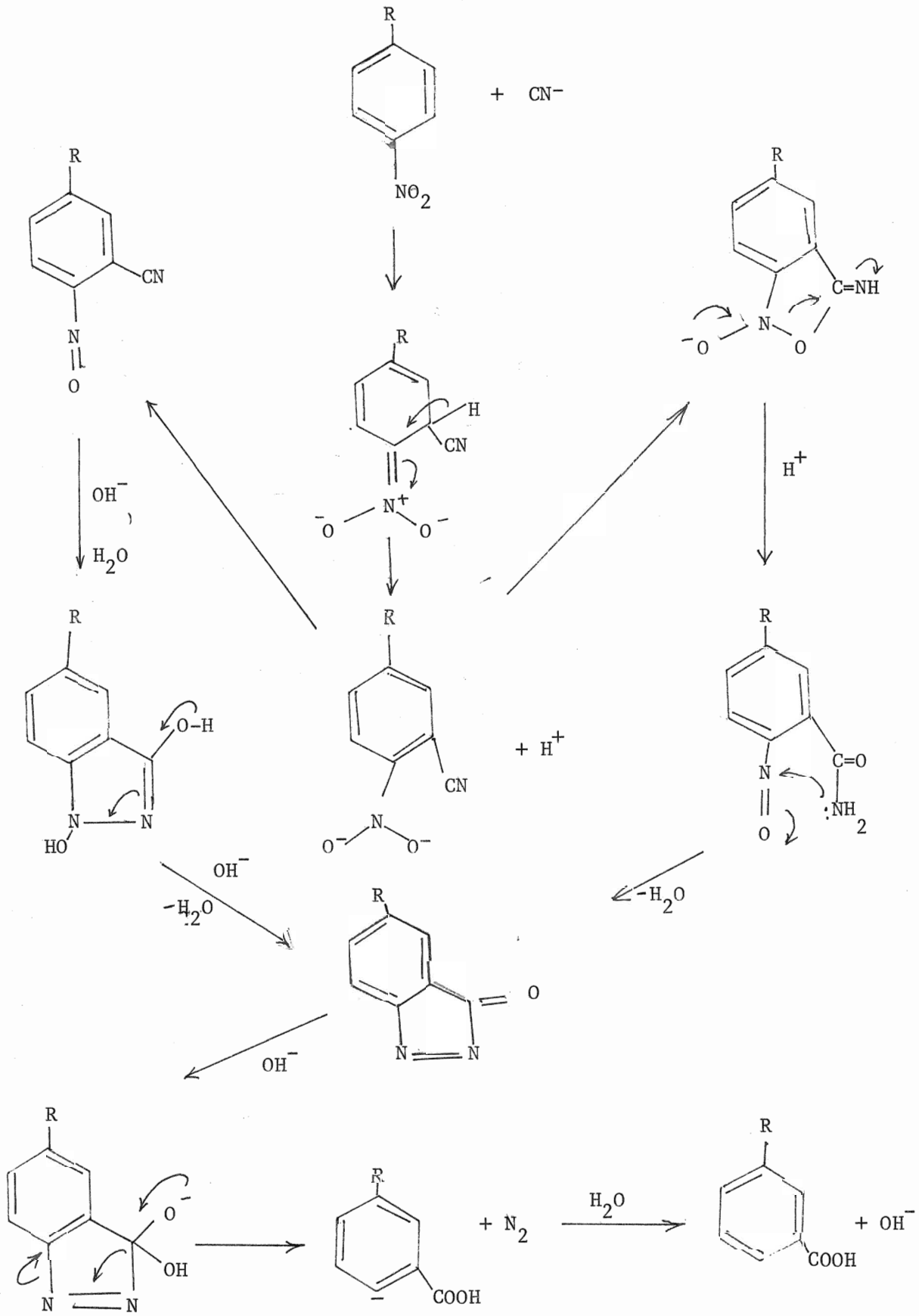
The orientation was explained after Roberts[5] proposed that the inductive effect of the substituent controlled the direction of addition to a 3-substituted aryne (V). When the 3-subsituent was inductively electron-withdrawing, as both OCH_3 and CF_3 are,



(V) (VI) (VII)

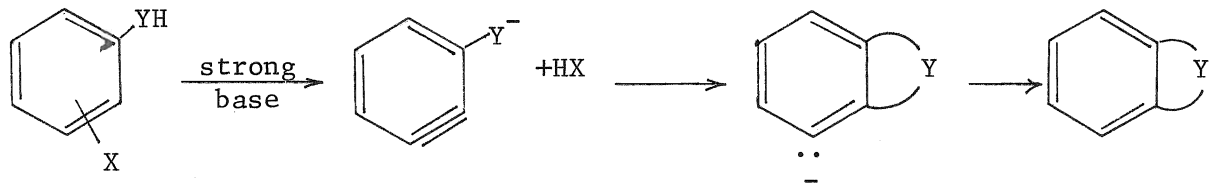
it would favour transition state (VI) for addition at the more remote position because the negative charge is localized on a carbon adjacent to the substituent. The alternate transition state (VII) is favoured when the substituent R is electron-donating. Orientation is less specific when R is a methyl group (both ortho and meta products are obtained), which is consistent with this interpretation.

Cine-substitution in reactions involving some arynes is sometimes useful synthetically, for example, in making some amines that would be difficult to make in other ways. However, cine-substitution does not necessarily mean an aryne mechanism. The conversion of various aromatic nitro-compounds to carboxylic acids under the influence of alcoholic potassium cyanide (Von Richter[6] reaction) is not thought to involve aryne intermediates; the following mechanism is consistent with the known facts[7]:


R
+ CN⁻
NO2
CN
N
O
OH⁻
H2O
H
CN
N+
O⁻
O⁻
C=NH
N
O
O
H+
O-H
N
N
HO
+ H+
CN
N
O⁻
O⁻
C=O
N
O
NH2
OH⁻
-H2O
-H2O
O
N
N
OH⁻
O⁻
OH
N
N
+ N2
H2O
COOH
+ OH⁻
COOH

Ring Closure Via Aryne Intermediates

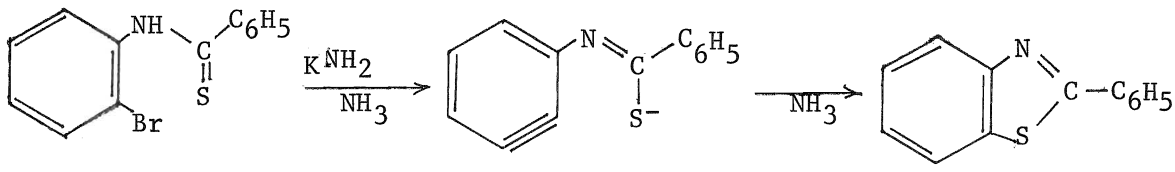
A synthetic application pregnant with potentialities is ring closure *via* aryne intermediates. The main objective in such ring closures is to create an intermediate which has both an aryne "triple bond" and a strong nucleophile suitably located in a side chain. The nucleophile can then add intramolecularly to the aryne structure, and finally a proton will be acquired. (The reaction sequence is shown diagramatically in scheme 1).



Scheme 1

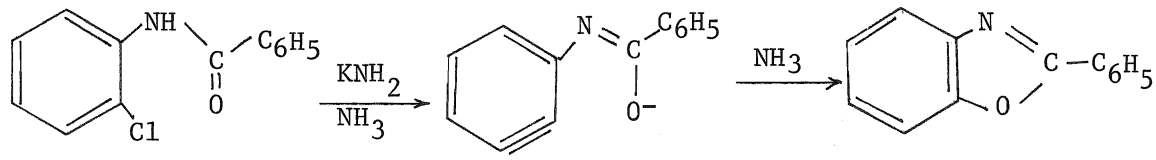
A variety of side chain nucleophiles have been incorporated in this scheme, often with potassium amide in liquid ammonia as the base. The following syntheses, presented by Bunnett and Hrutfiord, are illustrative.

2-phenylbenzothiazole (IX)[8]



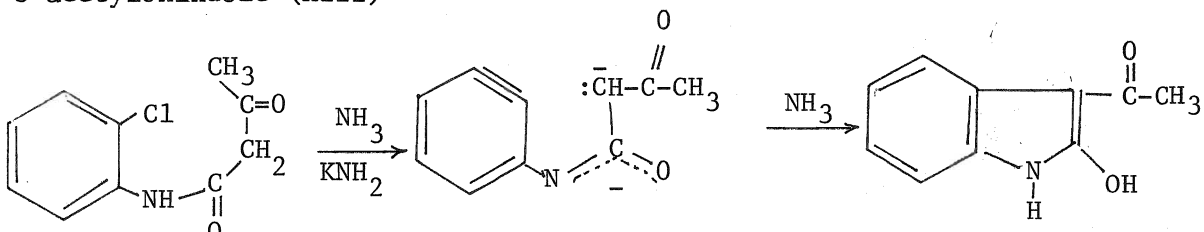
(VIII) (90%) (IX)

2-phenylbenzoxazole (XI)[9]



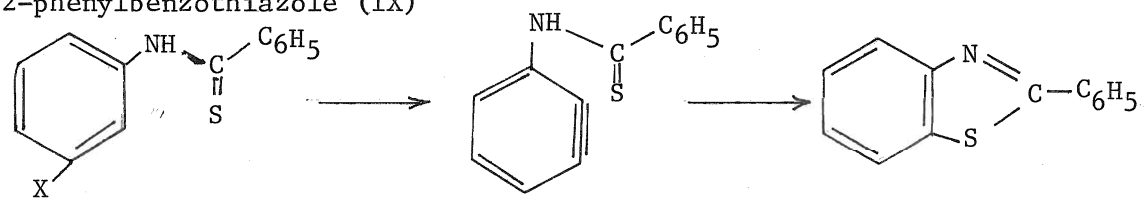
(X) (69%) (XI)

3-acetyloxindole (XIII)[9]



(XII) (XIII) yield 86%

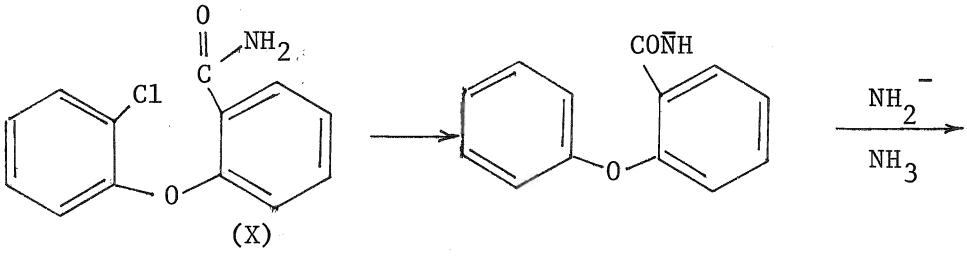
2-phenylbenzothiazole (IX)[10]



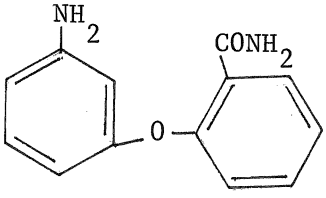
(XIV) a,X = Br (a, 72%) (IX)

b,X = Cl (b, 67%)

A difficulty with the scheme is that the aryne intermediate is sometimes attacked by an external amide ion, rather than by the side-chain nucleophile; resulting in a simple amination product as in this case.[11]



(X)



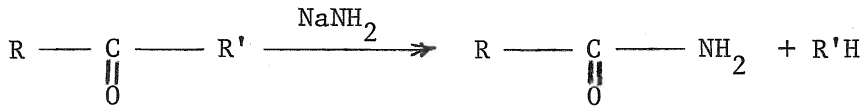
(55%) (XI)

Nevertheless, the scheme is of great general use, and the side chains involved in such ring closures have included carbon, oxygen, nitrogen and sulphur as the nucleophilic atom.

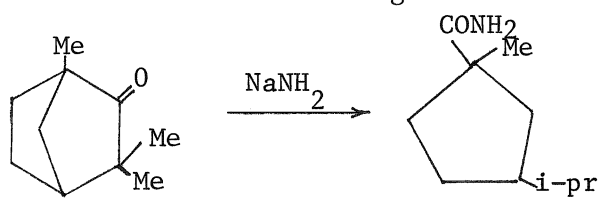
The potential problem in developing these ring-closure reactions to halogen-containing non-enolizable ketones is the possibility of Haller-Bauer scission of the ketone.

(ii) HALLER-BAUER SCISSION

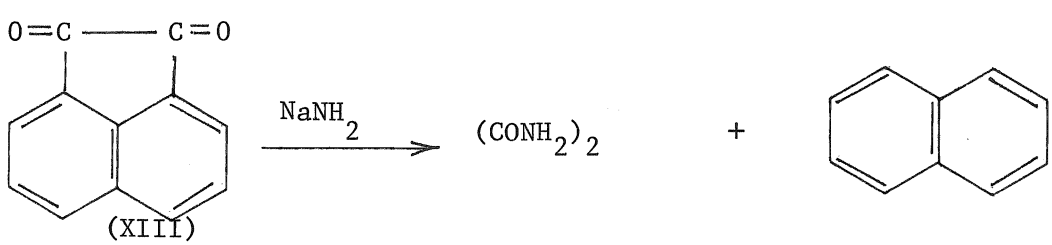
The Haller-Bauer reaction has been known for nearly 70 years. The original reaction consisted of the action of sodium amide on a non-enolizable ketone, causing cleavage of a carbon-carbon bond and resulting in the formation of an amide and a hydrocarbon.



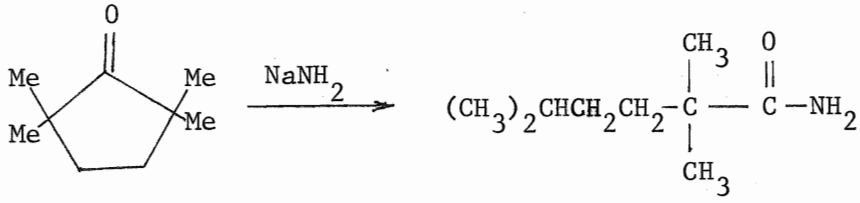
In 1906, Semmler[12] discovered the cleavage reaction in connection with his investigation of the structure of fenchone (XII), but he did not explore this reaction further. Two years later, Haller and Bauer examined these reactions in more detail and isolated benzamide from the treatment of benzophenone with sodium amide in boiling benzene or toluene[13]. Since that time, various ketones, e.g. (XIII)[14], (XIV)[15] and (XV)[16], have been shown to undergo the reaction.



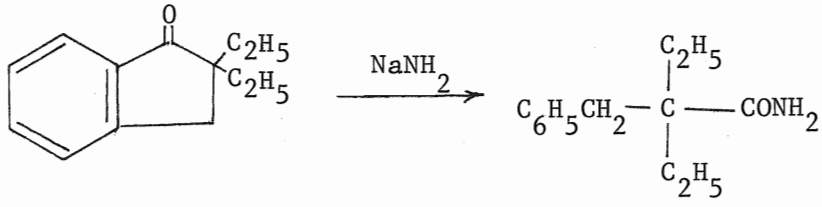
(XII)



(XIII)



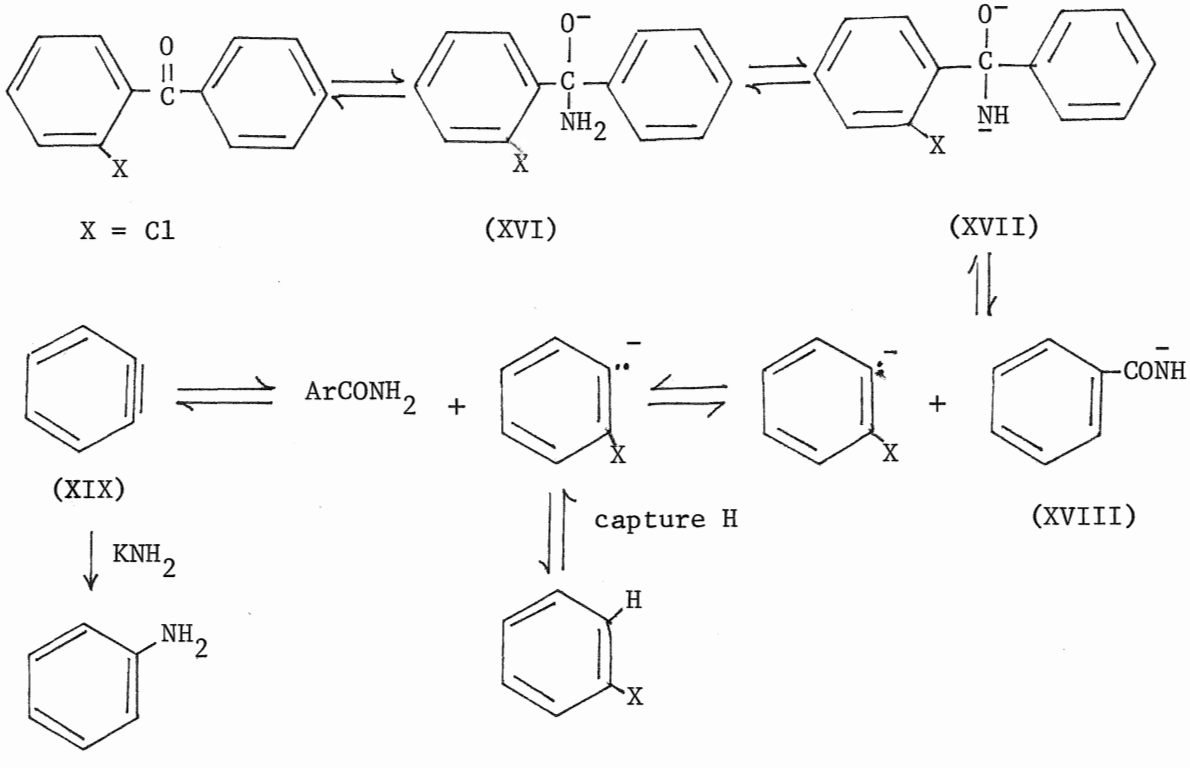
(XIV)



(XV)

(a) Low-temperature Haller-Bauer Scission

In 1962, Bunnett and Hrutfiord[17] showed that 2-chlorobenzophenone is readily split by action with potassium amide in refluxing liquid ammonia (-33°), although benzophenone is stable under these conditions. They suggested the reaction proceed as follows (scheme 2):

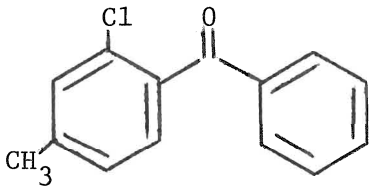


scheme 2

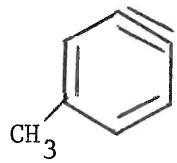
When the 2-chlorophenyl anion is formed, it can readily lose the chloride ion to give aryne (XIX), which will easily accept ammonia or amide ion to give aniline, i.e. one of the main products.

The halogen present in the ortho-halogenophenyl anion strongly affects aryne formation. It is found that the order of reactivity of aryl halides with potassium amide in liquid ammonia is Br > I > Cl >> F[4]. Fluorobenzene does not yield aryne at -33°, but it quickly exchanges ortho hydrogen with potassium amide in ammonia. Bromobenzene does not exchange without undergoing loss of bromide ion, and chlorobenzene shows intermediate behaviour. These results show that elimination is initiated by removal of a proton from the ortho position by NH_2^-. The resulting o-halogenophenyl anion may either lose halide ion to yield aryne or recapture a proton from the solvent. If the halogen is bromine, the halide ion is lost, if it is fluorine, a proton is recaptured; and if it is chlorine, reactions of each type occur. These observations explain why 2-chlorobenzophenone gives aniline as one main product, whereas 2-fluorobenzophenone gives fluorobenzene. When a 2-fluorophenyl ion is formed, it is protonated to give fluorobenzene, rather than losing a fluoride ion, to give aryne (XI).

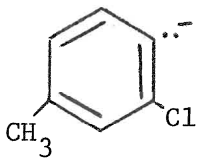
When 2-chloro-4-methylbenzophenone (XX) is treated with potassium amide under these conditions, the product contains 2-toluidine. If only 4-methylbenzyne (XXI) was produced, 3- and 4-toluidines would be formed, but not 2-toluidine. Thus, (XX) should give anion (XXII) initially, which might expel chloride ion to give aryne (XXI) or capture a proton to give 3-chlorotoluene from which all three toluidines can be formed.



(XX)



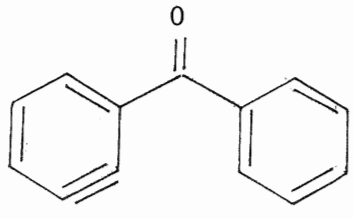
(XXI)



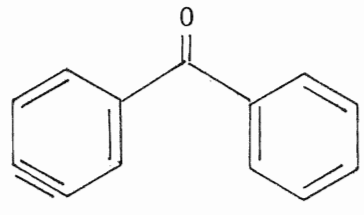
(XXII)

3- and 4-Chlorobenzophenone both undergo little splitting when treated with potassium amide in ammonia and so it should be possible to predict the products of reaction by using Robert's rule[5a]. Thus a 3-substituted aryne should give preferentially a 3-substituted product if the substituent is inductively electron-attracting and a 2-substituted product if the substituent is electron-releasing. A 4-substituted aryne should give preferentially a 4-substituted product if the substituent is electron-attracting and a 3-substituted product if it is electron-releasing, though the effect is much less marked than in the case of a 3-substituted arynes. This rule has been used to explain the products obtained when 3- or 4-chlorobenzophenone is treated with potassium amide in liquid ammonia.

In terms of intermediates (XXIII) and (XXIV), these reactions would be explained by Bunnett and Hrutfiord in the following way[17].



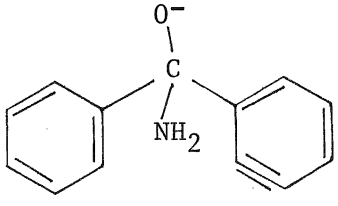
(XXIII)



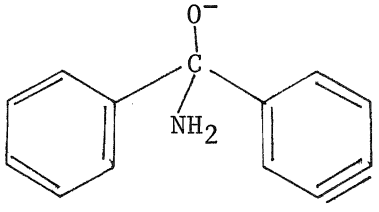
(XXIV)

3-Aminobenzophenone would be mainly expected from (XXIII), and (XXIV) should yield 4-aminobenzophenone and 3-aminobenzophenone (in approximately equal quantities). Since 4-chlorobenzophenone would only give (XXIV), the reaction product should be the 3- and 4-substituted compound

in approximately equal parts. [Since 3-chlorobenzophenone yields no 4-aminobenzophenone, it would be assumed that this compound does not react through (XXIV); from reaction through (XXIII), one would expect 3-aminobenzophenone to be the main product of this reaction.] But the experimental results show that 3- and 4-chlorobenzophenones add amide ion predominantly at the position nearer the carbonyl group and hence the mechanism outlined above is not correct. Bunnett and Hrutfiord [17] therefore considered the possibility that intermediates (XXV) and (XXVI) are formed; these are derived by addition of amide ion to the carbonyl function to produce the group $-C(NH_2)(C_6H_5)O^-$. As this group is electron-releasing, it should favour addition of nucleophile to the aryne function at the position nearer to the substituent, as is observed in fact:

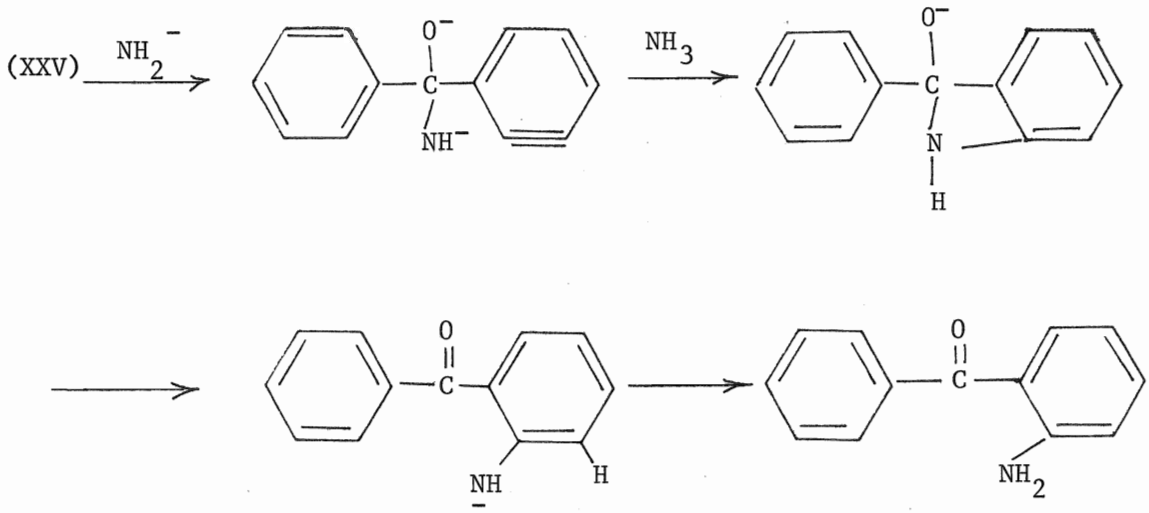


(XXV)



(XXVI)

Another possibility open to (XXV), which was considered[17], is that intramolecular addition occurs as sketched, forming 2-aminobenzophenone. (scheme 3)



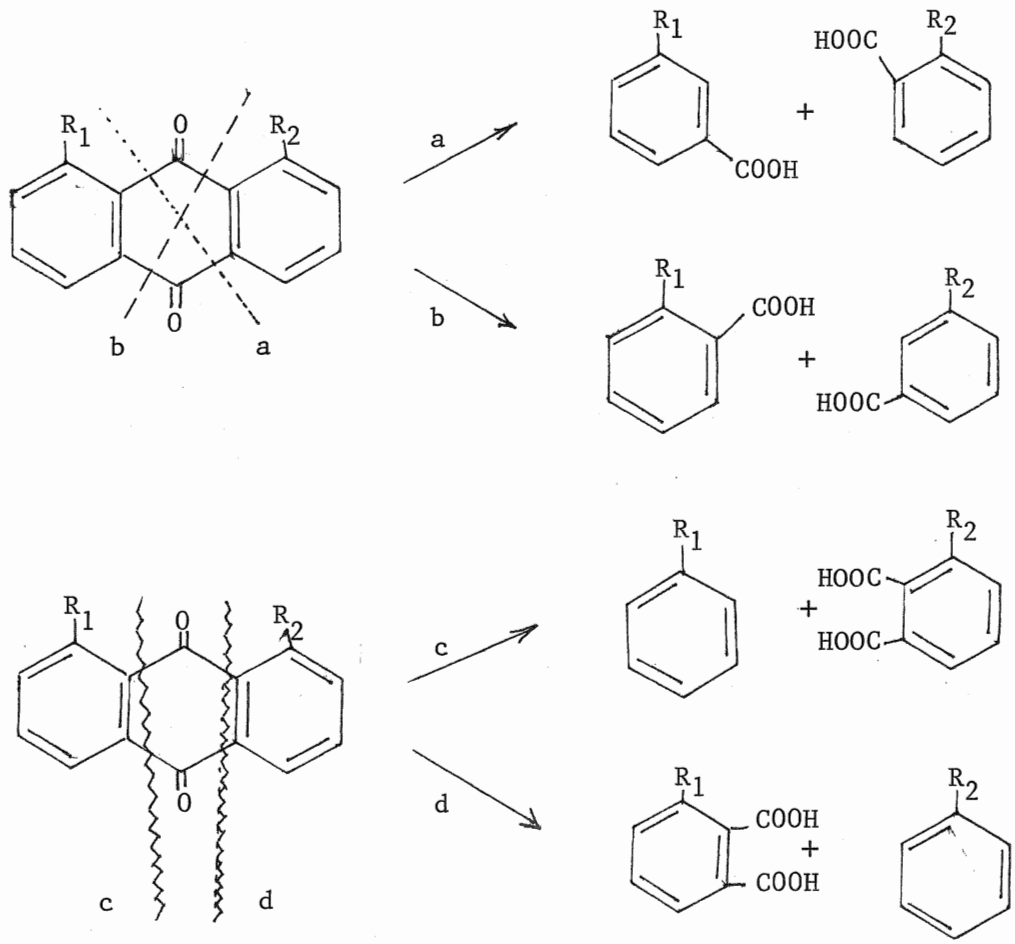
scheme 3

(b) <u>High-temperature Haller-Bauer Scission</u>

In 1971, Davies, Derenberg and Hodge[18] showed that benzophenone and a number of other non-enolizable ketones are split by treatment with potassium tert-butoxide:water mixture. This research was published while the work described in this thesis was being done, and involved different reaction conditions.

In a second paper[19], the successful cleavage of mono-substituted anthraquinones was reported, (anthraquinones are more resistant to cleavage by base than many other types of non-enolizable carbonyl compounds).

Anthraquinones can, in principle, be cleaved in four ways by potassium t-butoxide:water mixture. (scheme 4)



scheme 4

Cleavage by paths (a) and (b) afford substituted benzoic acids and cleavage by paths (c) and (d) afford substituted phthalic acids and non-acidic fragments. The results of these experiments are shown in Table I.

TABLE I

Cleavage of anthraquinones by tert-butoxide:water[19]

Substituent(s)	Reaction time(t/h)[a]	Yield (%) of acids(b)	Acid (s) product[c]	Composition (%) of the acid fraction[d]
None	2	60[e]	Benzoic	97
	4	98	Phthalic	3
1-chloro	2[f]	90	Benzoic	23
	2	96	3-chlorobenzoic	32
			Phthalic	45
2-chloro-	2	97	Benzoic	39
			3-chlorobenzoic	39[g]
			4-chlorobenzoic	
			Phthalic	22

a. Reactions carried out at reflux temperature (ca. 85°) unless indicated otherwise.

b. Calculated assuming the acid fraction had the composition given in the last column.

c. Acids are listed in order of increasing retention times of the corresponding esters. (Apiezon L; 195°)

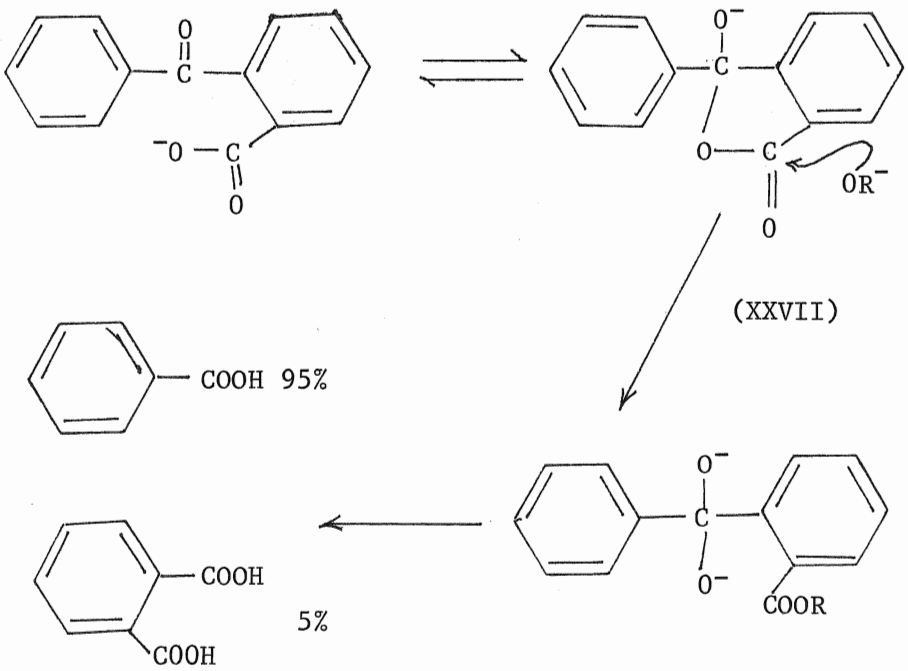
d. Determined by g.l.c. of the methylated acid fraction. Results are probably accurate to within 3%.

e. 31% starting material recovered.

f. Reaction carried out at 20°.

g. Methyl 3- and 4-chlorobenzoates were not resolved under g.l.c. conditions. I.r. spectral analysis indicated that both isomers were present and that the 4-chloro-isomer was the more abundant.

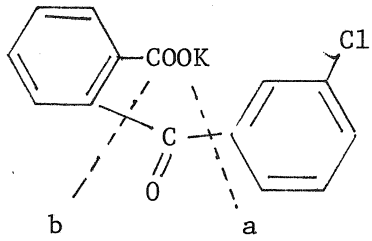
It was also noted in these experiments that cleavage of benzophenone-2-carboxylic acid occurred very rapidly under the same conditions. The reason for this easy cleavage can be illustrated by scheme 5, in which one mole of hydroxide or butoxide is required; the carboxylate anion is thought to be involved, forming a cyclic intermediate (XXVII).



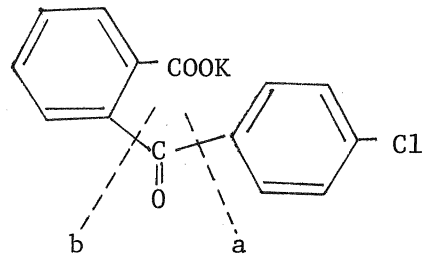
R = H, or Bu^t

scheme 5

1-Chloroanthraquinone was cleaved more readily to form phthalic acid than 2-chloroanthraquinone (Table I). Davies and Hodge[19] suggested 1-chloroanthraquinone was cleaved to (XXVIII), by cleavage of the carbonyl group nearer the substituent group, and 2-chloroanthraquinone was cleaved preferentially to (XXIX).



XXVIII

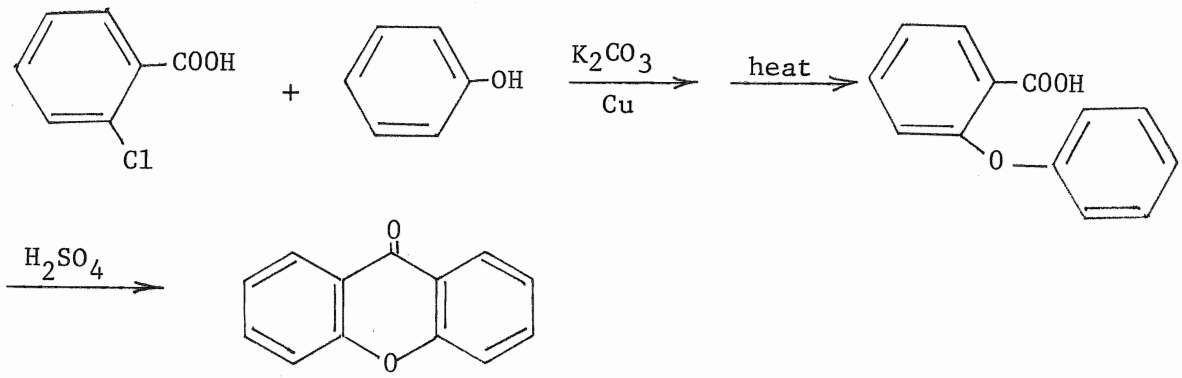


XXIX

After the initial step, cleavage of (XXVIII) occurred more frequently at the (a) position than the (b) position, but cleavage of (XXIX) occurred more frequently at the (b) position than at the (a) position.

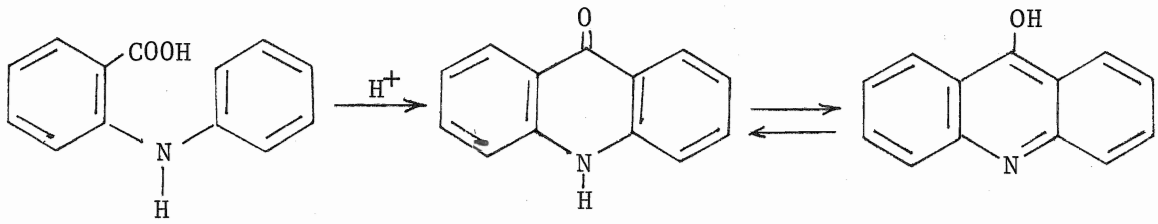
(iii) SYNTHESIS OF XANTHONES, THIOXANTHONES AND ACRIDONES

Xanthones, thioxanthones and acridones have certain approaches to synthesis in common. For example, in 1906, Ullmann[20,21] prepared xanthone from 2-chlorobenzoic acid and phenol by treatment with potassium carbonate and a trace of copper at elevated temperature, followed by reaction of the resultant 2-carboxydiphenyl ether with concentrated sulphuric acid.



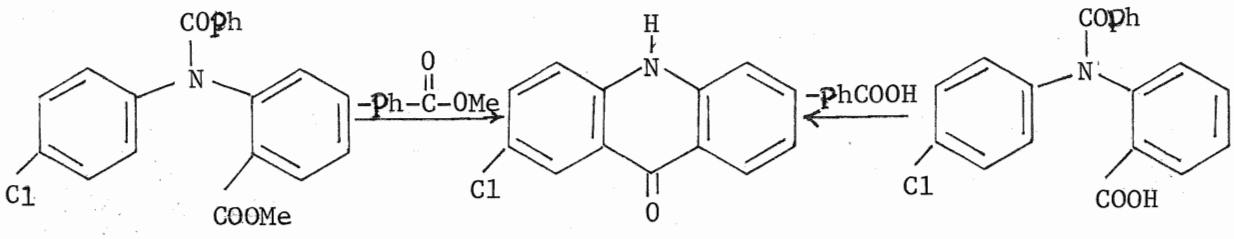
Mayer[22] used the same technique as Ullmann to prepare 2-carboxydiphenyl sulphide, and cyclised this intermediate to make thioxanthone.

A widely-used method for the preparation of acridones involves the ring-closure of diphenylamine-2-carboxylic acids by means of sulphuric acid[23], polyphosphoric acid[24], or phosphorus oxychloride followed by hydrolysis of the resulting 5-chloroacridine by dilute hydrochloric acid[24].



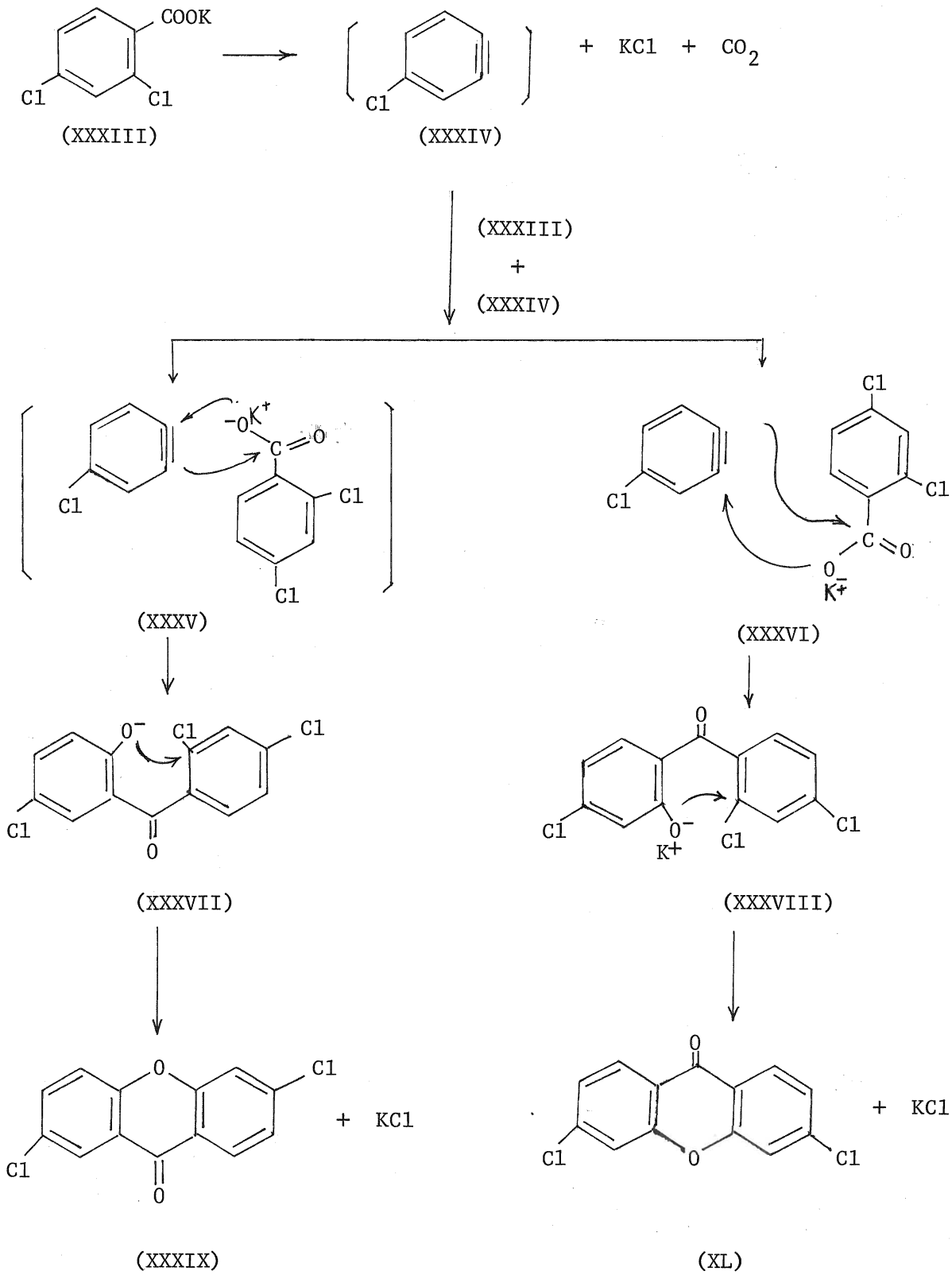
These syntheses involve heating the intermediates with acidic reagents to effect ring-closure. In other syntheses, ring closure is directly achieved by heating. For example, some esters (XXX) readily

lose methyl benzoate in heating, and some acids (XXXI) lose benzoic acid on heating to give, in each case, the corresponding acridone[25].

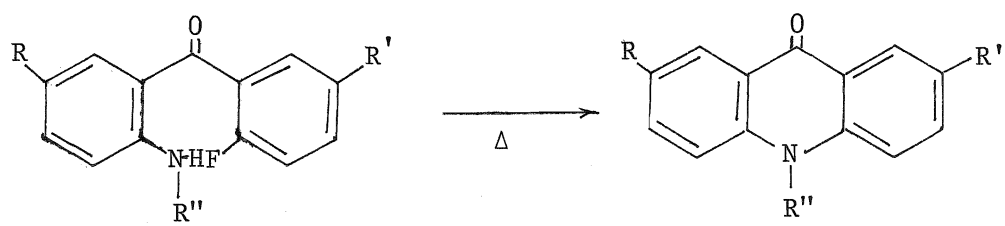


(XXX) (XXXII) (XXXI)

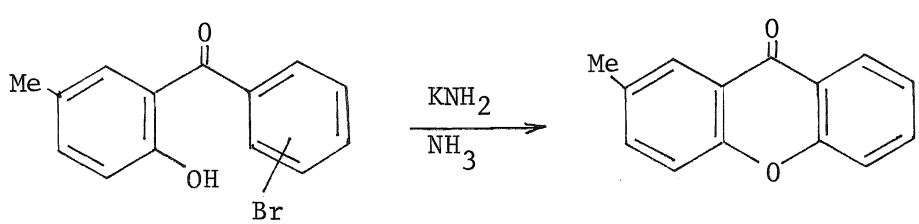
The pyrolysis of o-chlorobenzoates has been used by Kochi[26] in 1963 in a synthesis of xanthone. It has been suggested that this reaction proceeds <u>via</u> benzyne as an intermediate:[27,28] a scheme is shown on page 19.


COOK
Cl
Cl
(XXXIII)
Cl
(XXXIV)
+ KCl + CO_2
(XXXIII)
+
(XXXIV)
$-O^{K+}$
C
O
Cl
Cl
Cl
(XXXV)
Cl
Cl
Cl
C
O
O
K^+
(XXXVI)
O^-
Cl
Cl
Cl
O
(XXXVII)
O
Cl
Cl
O^-
K^+
Cl
Cl
(XXXVIII)
O
Cl
Cl
+ KCl
(XXXIX)
O
Cl
Cl
O
+ KCl
(XL)

In general, basic methods have not been extensively examined for ring-closure. Meisenheimer and co-workers[29] have reported a preparation of xanthone from 2-hydroxy-2'-chlorobenzophenone, and Sternbach and co-workers[30] synthesised acridones from 2-amino-2'-fluorobenzophenones. These compounds undergo internal nucleophilic displacement of fluorine to give high yields of the corresponding 9-acridones.



Walthew[31] has prepared 3-methylxanthone, though the details have not yet been published in the literature, by the following method.



The conditions used were essentially those of Bunnett and Hrutfiord[17], and no significant Haller-Bauer scission was noted for the ortho-bromo-compound.

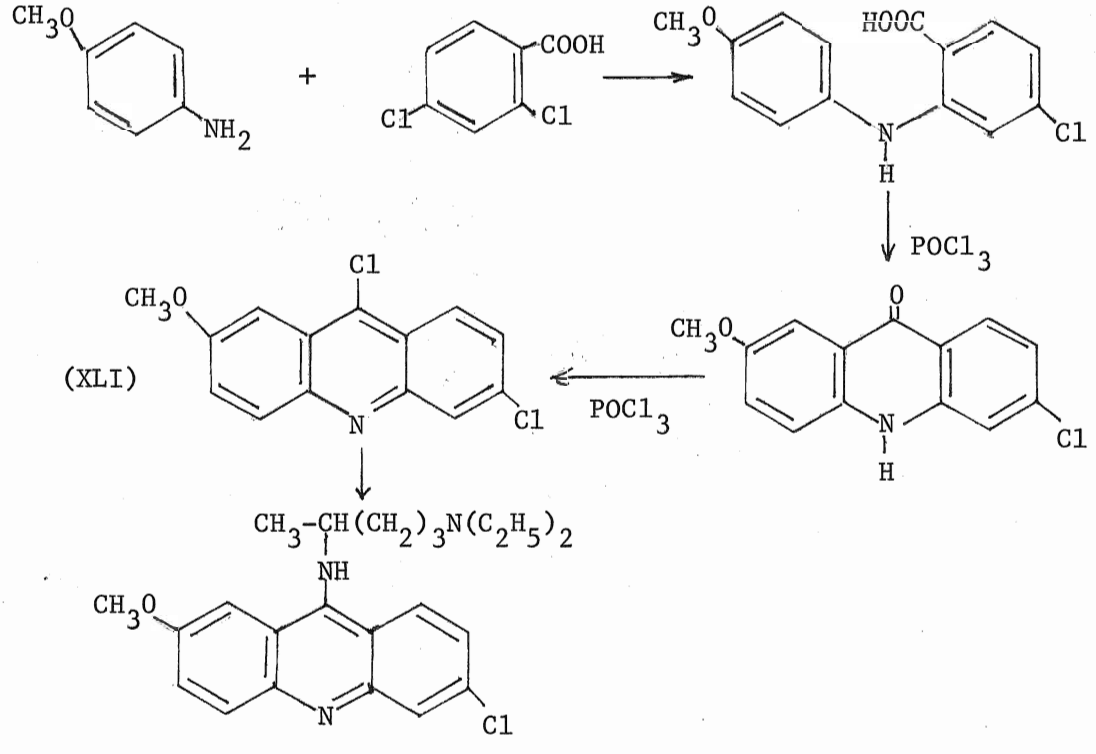
The last synthesis and the work of Bunnett and Hrutfiord bear directly on the objectives of the research described in this thesis. These objectives are: (i) to investigate the feasibility of synthesising acridones from suitable derivatives of 2-amino-2'-and -3'-halogenobenzophenones and (ii) to investigate the feasibility of using tricyclic chloro-ketones for syntheses of heterocyclic compounds.

D I S C U S S I O N

SECTION I

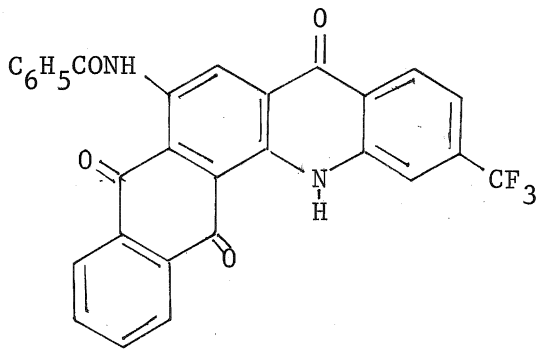
ROUTES TO ACRIDONE FROM DERIVATIVES OF 2-AMINO-2'- AND 3'-HALOGENOBENZOPHENONES

Acridine derivatives have been of interest for a considerable period of time. For example, quinacrine[32] (XLII), also called mepacrine, Atebrin, or 2-methoxy-6-chloro-9(4'-diethylamino-1'-methyl butyl)-aminoacridine, is a valuable antimalarial drug. A commercial synthesis proceeds via (XLI), which is condensed with the appropriate amine to give quinacrine (XLII). Although quinacrine has been widely used as a clinical suppressive, it is not the ideal antimalarial drug.



Other acridines have attracted attention as medicinals, e.g., acriflavine (3,6-diamino-10-methylacridinium chloride) against sleeping sickness and as an antibacterial agent, and Rivanol (3,9-diamino-7-ethoxyacridine) against amoebic dysentery.

Again, the useful acridine vat dyes, in which acridone and anthraquinone nuclei are fused by sharing a benzene ring in common, are fast and provide a wide range of colours. An example is Indanthrene Printing Blue F. G.[33] (XLIII) which is used in printing bright blue on calico.



(XLIII)

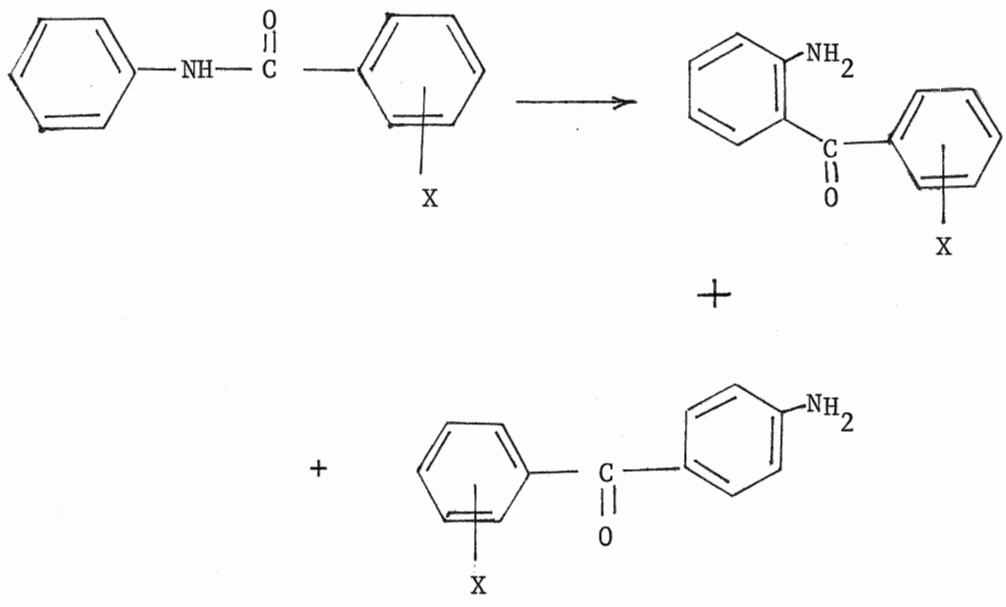
This section of the thesis is presented in two parts. The first deals with the synthesis of the required intermediates and the second with the reactions leading to the acridone system.

(i) Synthesis of Intermediates

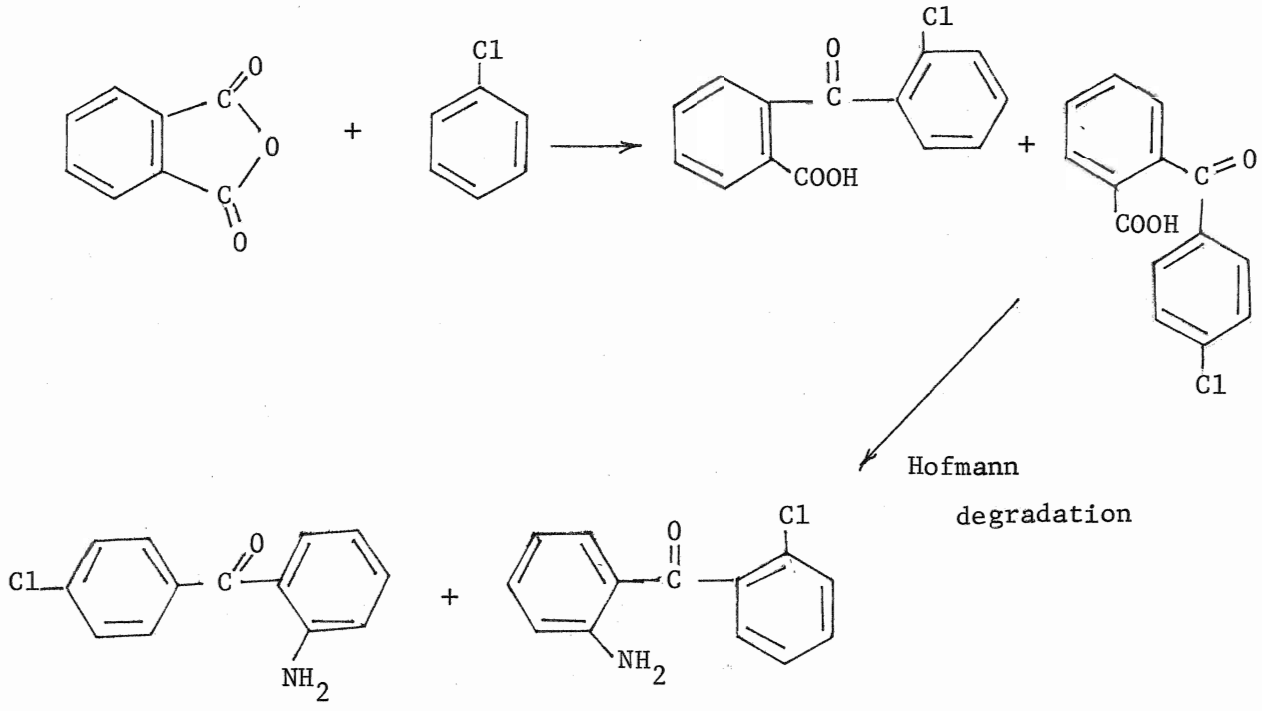
The compounds chosen for this investigation were 2-amino-2'-chlorobenzophenone and 2-amino-3'-chlorobenzophenone; both are seen to be derivatives of o-aminobenzophenone, bearing a chloro-substituent in the non-aminated benzene ring. Substituted o-amino-benzophenones are available by a number of methods, which include Fries rearrangement and Friedel-Crafts reaction.

However, these two standard methods suffer the disadvantage of being of limited value for synthesis where the chlorine must occupy a position ortho or meta to the ketone group because of orientation problems in the reactions in which the ketones are formed.

For example, Fries rearrangement:

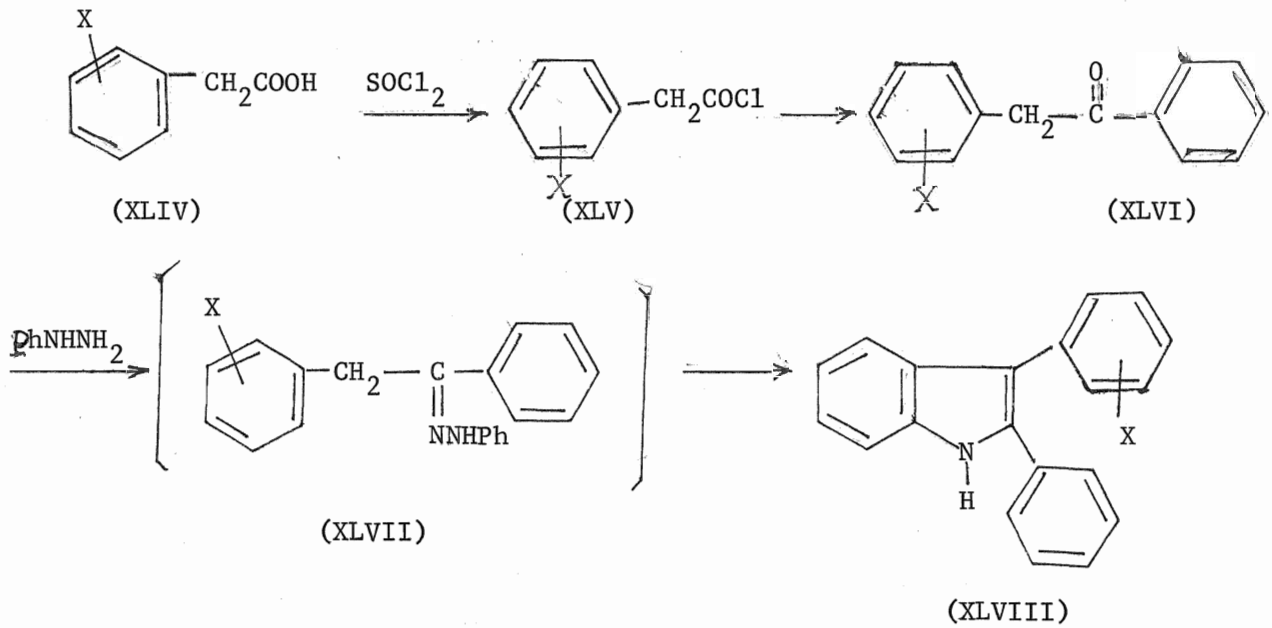


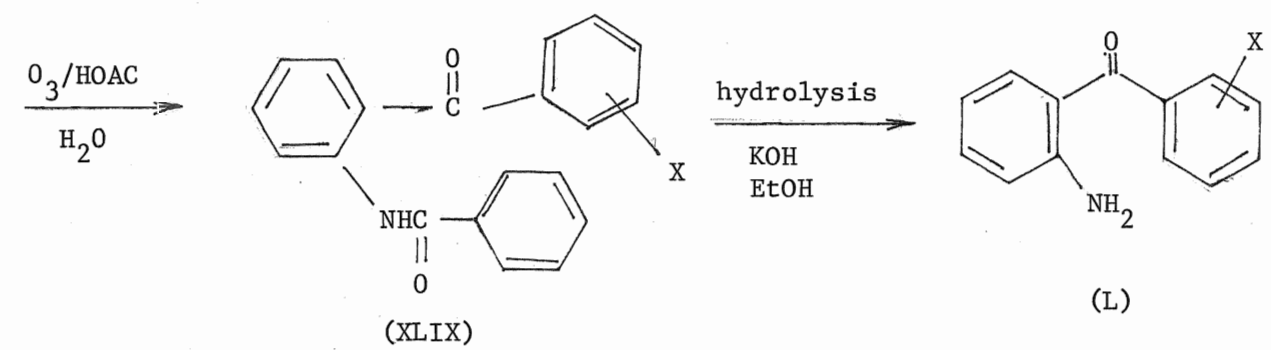
Friedel-Crafts reaction:



For this reason, it was decided to approach the synthesis by forming an appropriately substituted indole in which the position of the chlorine could be established independently by choice of starting materials and then to open the indole ring by oxidation so that the nitrogen atom of the indole ring eventually became the amino- or substituted amino-group of the benzophenone.

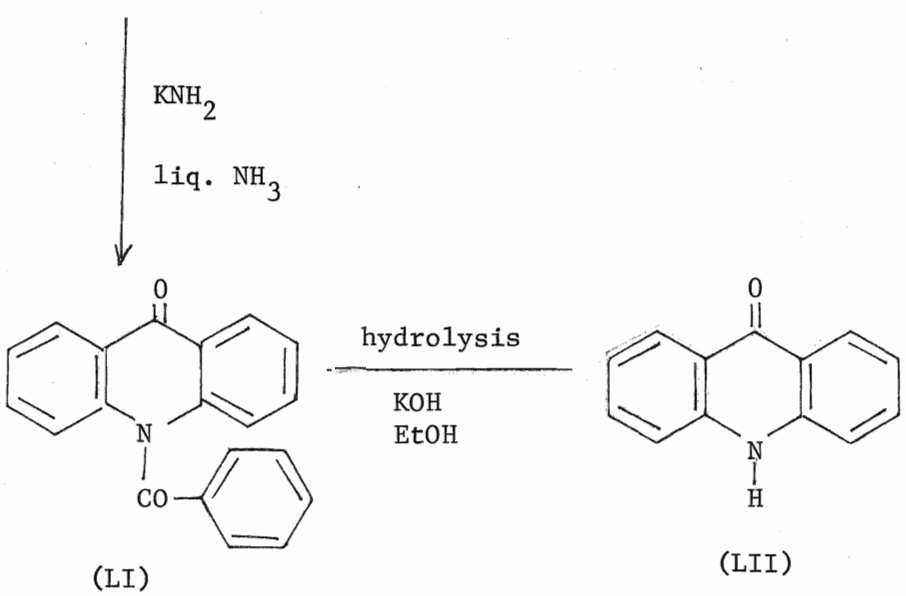
The general synthesis is outlined in scheme 6.





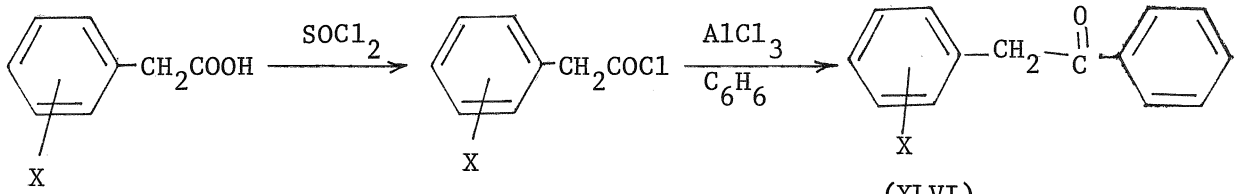
a,X = o-chloro-

b,X = m-chloro-



scheme 6

(a) Preparation of ω-(o-chlorophenyl)acetophenone (XLVIa) and ω-(m-chlorophenyl)acetophenone (XLVIb)

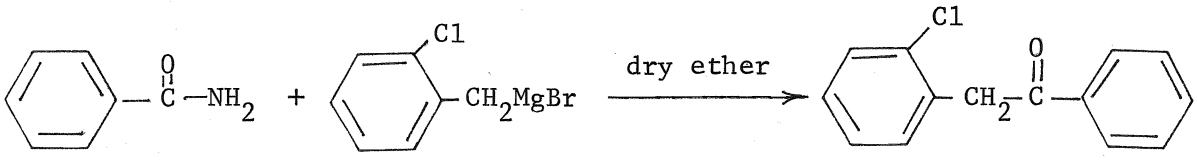


(XLIV) (XLV) (XLVI)

a,X = o-chloro-

b,X = m-chloro-

ω-(o-Chlorophenyl)acetophenone (XLVIa) has been prepared by reaction of benzamide (LIII) with o-chlorobenzylmagnesium bromide (LIV)[34]. This yield was 73%, m.p. 70.5°.



(LIII) (LIV) (XLVIa)

The Friedel-Crafts reaction has been used to make the ketone (XLVIb). m-Chlorophenylacetic acid (XLIVb) was treated with thionyl chloride to make m-chlorophenylacetyl chloride (XLVb); after removing excess thionyl chloride, the crude product was condensed with benzene in presence of aluminium chloride to give (XLVIb), m.p. 43° in 74% yield[35]. In the present work, the Friedel-Crafts reaction was used to prepare both ketones. The yield of (XLVIa) was 77%, m.p. 69° and of (XLVIb) was 65%, m.p. 39-41°.

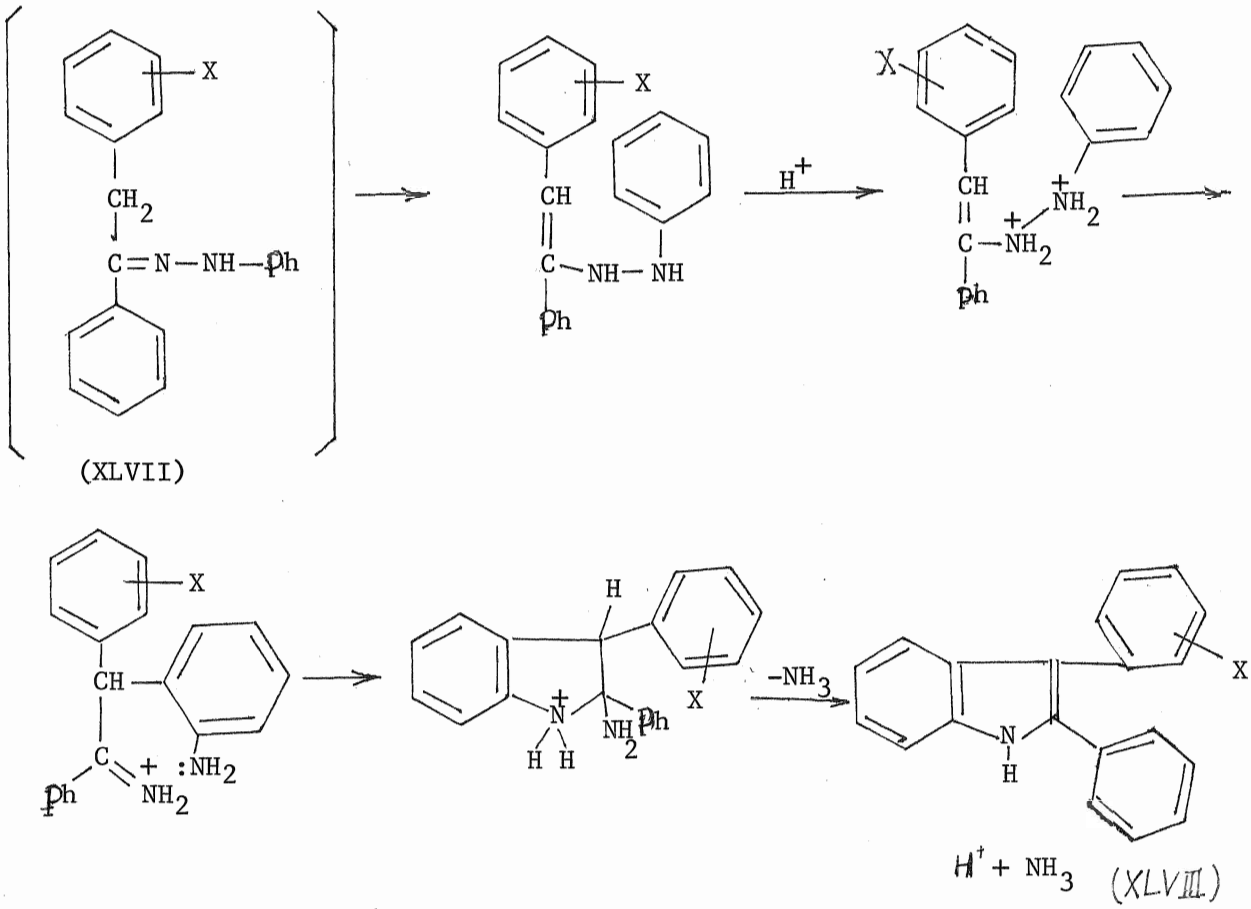
The mass spectra of the ketones (XLVIa) and (XLVIb) showed parent peaks of very low intensity at high voltage (70 e.v.). The low voltage mass spectra (24 e.v.), however, showed the presence of parent peaks at m/e = 232 (M^+, ^{37}Cl) and 230 (M^+, ^{35}Cl) [peak ratio ∿ 1:3] for compound (XLVIa), and for compound (XLVIb) at m/e = 232 (M^+, ^{37}Cl), 230 (M^+, ^{35}Cl) [peak ratio ∿ 1:3]. The low voltage spectra have very clean parent peaks, which were not seen definitively at the higher voltage. Higher ionization energies caused complete cleavage of the molecular ion.

Identification of these compounds (XLVIa) and (XLVIb) was assured by other spectroscopic techniques, such as n.m.r. and i.r.

(b) Preparation of 2-Phenyl-3-(2-chlorophenyl)indole (XLVIIIa) and 2-Phenyl-3-(3-chlorophenyl) indole (XLVIIIb)

2-Phenyl-3-(2-chlorophenyl)indole (XLVIIIa), was prepared by an application of the Fischer method[36]. Robinson has pointed out[37] that in the Fischer indole synthesis, it is generally assumed that the last intermediate in the mechanistic sequence is a 2-aminoindoline which forms the indole nucleus by elimination of amine.

The crude phenylhydrazone (XLVIIa), formed from ketone (XLVIa) and phenylhydrazine, was cyclised by heating with a mixture of concentrated hydrochloric acid and methanol for two days on a steam bath. The solvent was removed under reduced pressure and the product was



a,X = o-chloro-

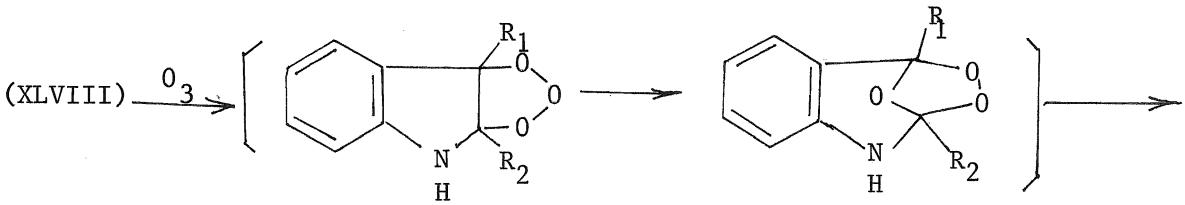
b,X = m-chloro-

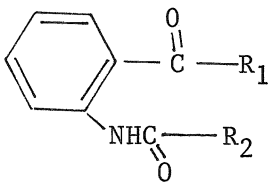
separated and extracted with methylene chloride. The compound was finally obtained as a brownish crystalline solid, m.p. 138-141°, in 70% yield. A pure, colourless sample, was obtained by chromatography on Florisil.

2-Phenyl-3-(3-chlorophenyl)indole (XLVIIIb), was prepared by essentially the same procedure as that used for (XLVIIIa).

Crystallisation of the crude indole (XLVIIIb) from acetone - light petroleum (b.p. 30-60°) mixture gave a crystalline, but still impure, product. Separation by chromatography on Florisil and recrystallisation from hexane gave the pure indole (XLVIIIb). This compound (XLVIIIb) was obtained as pale yellow crystals in 49% yield, m.p. 114-115°, and its identity as (XLVIIIb) was confirmed by microanalysis, i.r., n.m.r. and mass spectra.

(c) Preparation of 2-Benzamido-2'-chlorobenzophenone (XLIXa) and 2-Benzamido-3'-chlorobenzophenone (XLIXb)





a, R_1 = o-chlorophenyl-

b, R_1 = m-chlorophenyl

R_2 = phenyl-

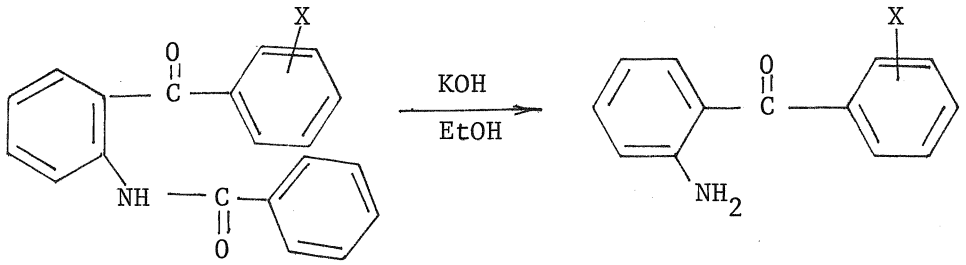
2-Benzamido-2'-chlorobenzophenone (XLIXa) was finally prepared by the complete ozonization of the indole (XLVIIIa) using a procedure based on that described by Sternbach and co-workers[38], although this procedure is not easily adaptable to large scale work. The procedure is described in detail in the Experimental Section. 2-Benzamido-2'-chlorobenzophenone (XLIXa) was separated from the crude reaction

product from ozonization of indole (XLVIIIa) by chromatography on Florisil. Compound (XLIXa) was obtained as in 36% yield. Some difficulty was experienced in the crystallization of this compound but the use of hexane was finally found to be satisfactory. The compound was obtained in an analytically pure state, but the mass spectrum showed a trace impurity corresponding to $C_{20}H_{14}ClNO_3$, suggesting possibly a small amount of the intermediate ozonide which could not be removed. However, this trace of impurity (LVIa), did not interfere with the next reaction.

2-Benzamido-3'-chlorobenzophenone (XLIXb) was prepared by essentially the same procedure as that used for (XLIXa). Crystallization of the crude (XLIXb) from hexane gave compound (XLIXb), which was purified further by chromatography on Florisil and obtained as pale plates in 42% yield. In this case, the mass spectrum gave no indication of trace impurity corresponding to $C_{20}H_{14}ClNO_3$.

Attempts to oxidize the indoles (XLVIII) with chromium tri-oxide in acetic acid[39] or with m-chloroperbenzoic acid[40] were not successful.

(d) Preparation of 2-Amino-2'-chlorobenzophenone (La) and 2-Amino-3'-chlorobenzophenone (Lb)

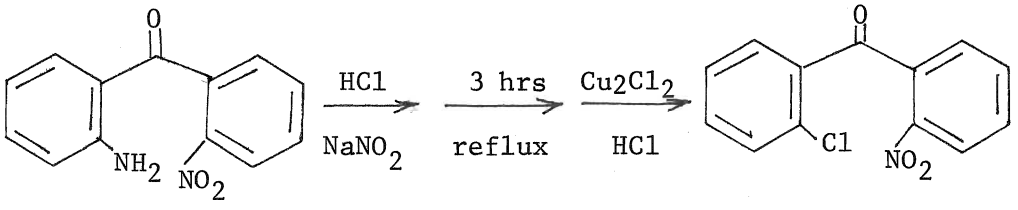


(XLIX) (L)

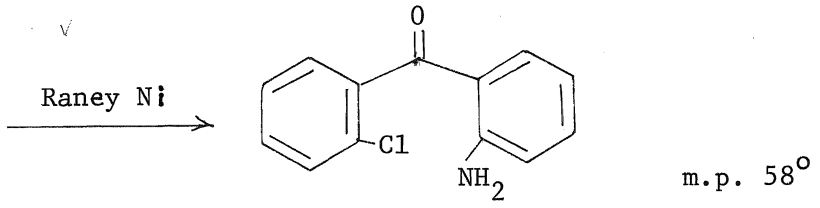
a, X = o-chloro-

b, X = m-chloro-

2-Benzamido-2'-chlorobenzophenone was hydrolyzed using potassium hydroxide solution in 95% aqueous ethanol to give 2-amino-2'-chlorobenzophenone (La), as pale yellow needles, m.p. 58°, in 36% yield. The product had the same melting point as that reported by Kariss and Newmark[41], whose synthesis is shown below. The i.r., n.m.r. and mass spectra are all consistent with structure (La).



m.p. 76-79°



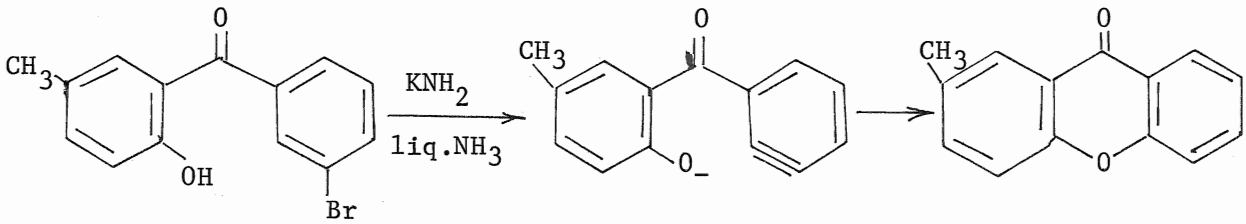
2-Benzamido-3'-chlorobenzophenone (Lb) was similarly hydrolyzed to give (Lb) in 66% yield. The amine was obtained pure by chromatography and crystallization, and its identity as (Lb) was confirmed by microanalysis, i.r., n.m.r. and mass spectra.

Acidic methods of hydrolysis of (La) and (Lb) were also examined, but were found to be less satisfactory than alkaline hydrolysis.

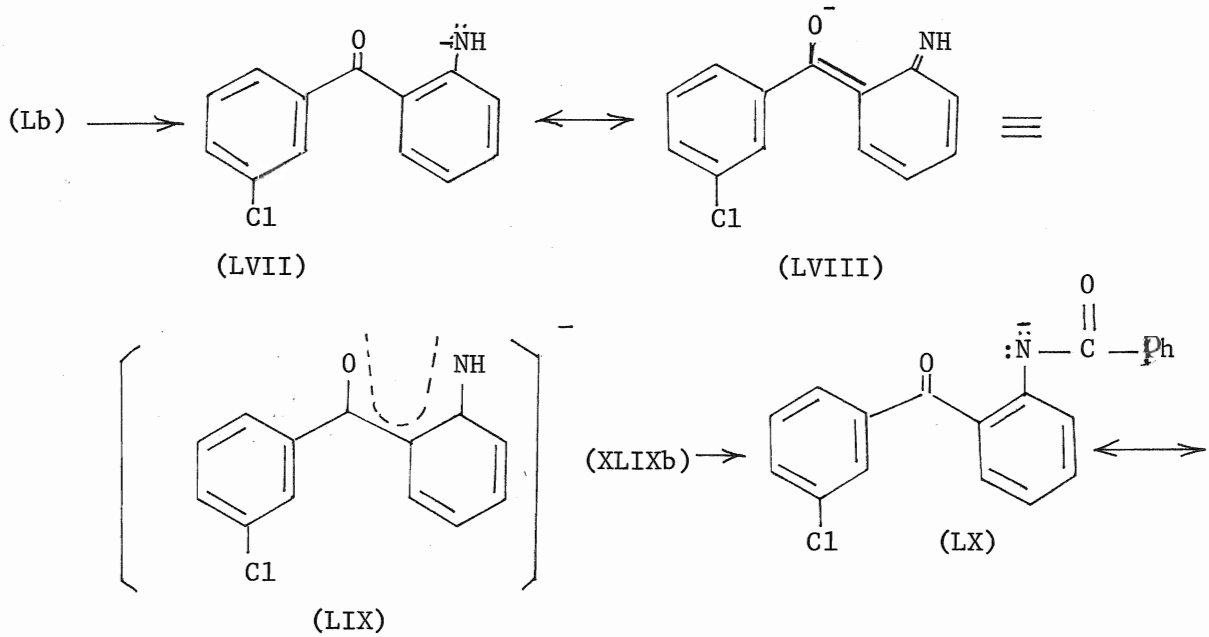
(ii) (a) <u>The Action of Potassium amide on 2-Benzamido-3'-chlorobenzophenones</u>

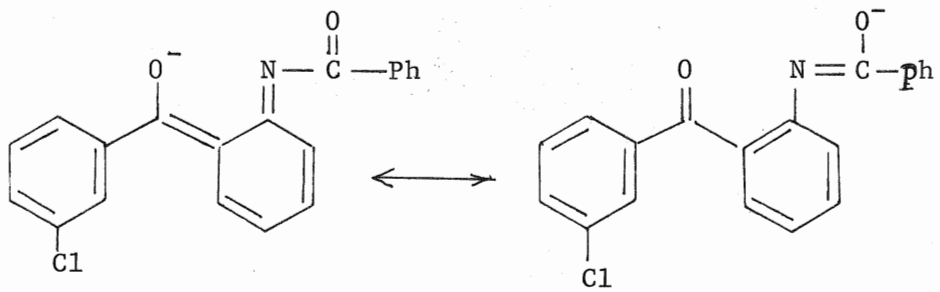
As described in the Introduction, Bunnett and Hrutfiord[17] discovered that 3-chlorobenzophenone reacted with potassium amide in ammonia to give 2- and 3-aminobenzophenones with apparently no accompanying Haller-Bauer scission. An aryne intermediate was suggested, in which the original carbonyl group had added amide ion and so become inductively electron releasing, to explain why 2-aminobenzophenone was the major product. Walthew[31] incorporated this result in a successful synthesis of 3-methylxanthone from 3-bromo-2'-hydroxybenzophenone by capturing the intermediate aryne intramolecularly by the phenolic group which was presumably present

as phenolate anion under the reaction conditions.



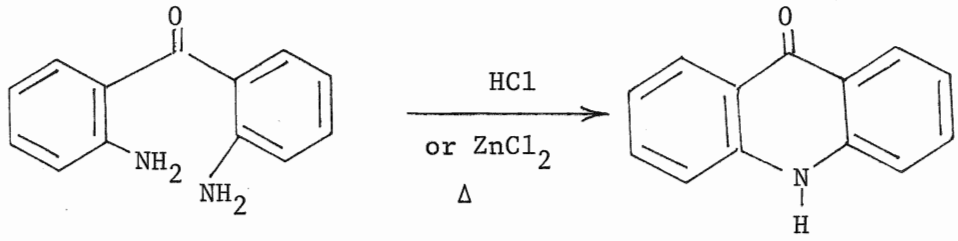
In the present work, an amino-group or benzoylamino-group might provide the nucleophilic nitrogen for intramolecular capture of the aryne. Such groups might well lose a proton in a strongly basic medium, to give an anilinate anion which, through delocalization, would increase the electron density at the carbon atom of the ketonic carbonyl group; external addition of amide ion to this carbonyl, as proposed for the experiments of Bunnett and Hrutfiord[17], might thus be inhibited, but the preferred site of addition of nucleophile to the aryne would still be <u>ortho</u> to the ketonic carbonyl group.



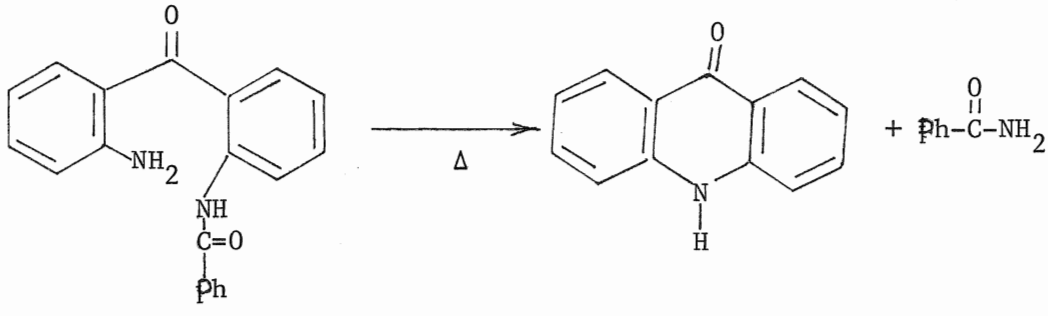


(LXI) (LXII)

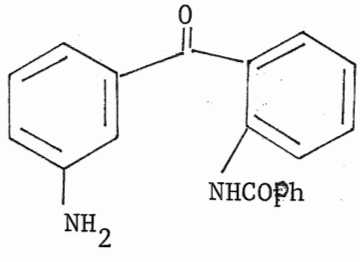
The compound chosen for examination was 2-benzamido-3'-chlorobenzophenone, which has been described earlier in this section. 2-Benzamido-3'-chlorobenzophenone (XLIXb) was added in ethereal solution to potassium amide in liquid ammonia, dried <u>in situ</u> (see experimental 1). After 4 hours, excess potassium amide was decomposed by adding ammonium chloride and the organic products were isolated using ether. This ethereal solution was first extracted with hydrochloric acid and then the acid solution was made alkaline to produce a brown crude solid which was separated and examined. Crystallization from n-propanol gave a yellow solid (21% yield), m. p. 234-236°; the infrared spectrum showed the presence of an amino group, and the mass spectrum showed m/e = 316 (molecular ion). This compound did not resolidify above its melting point; i.e. it was not apparently converted to acridone. Since Staedel has prepared acridone from 2,2'-diaminobenzophenone (LXIII), i.e. by heating under acidic conditions[42], it was tentatively assumed that 2-amino-2'-benzamidobenzophenone would similarly give acridone when heated.



(LXIII)



Compound (LXIV) would not however give acridone; for this reason, the yellow compound, m.p. 234-236°, is thought to be (LXIV).

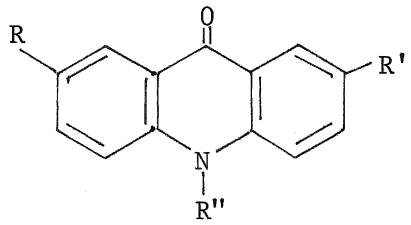


(LXIV)

The remaining ethereal solution was next extracted with aqueous sodium hydroxide to give a basic solution which was acidified with 2N hydrochloric acid; a brown tarry solid was formed which was not identified.

The residual ethereal layer was dried, evaporated, and the residue was crystallized, giving N-benzoylacridone (identified by infrared, ultraviolet, n.m.r. and mass spectra, and by microanalysis) in 36% yield, as yellow plates, m.p. 198-200°.

N-Benzoylacridone has a relatively low m.p. for an acridone though this is not unique for substituted acridones as seen from Table I (data from Sternbach and coworkers).[30]



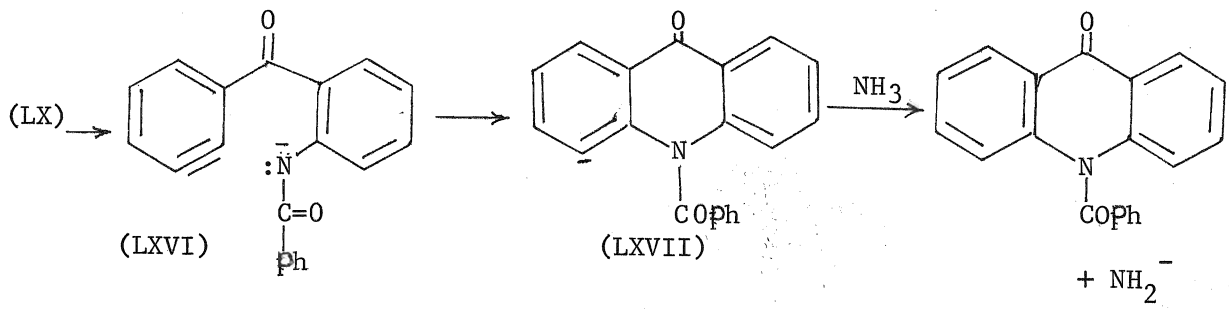
(LXV)

TABLE I

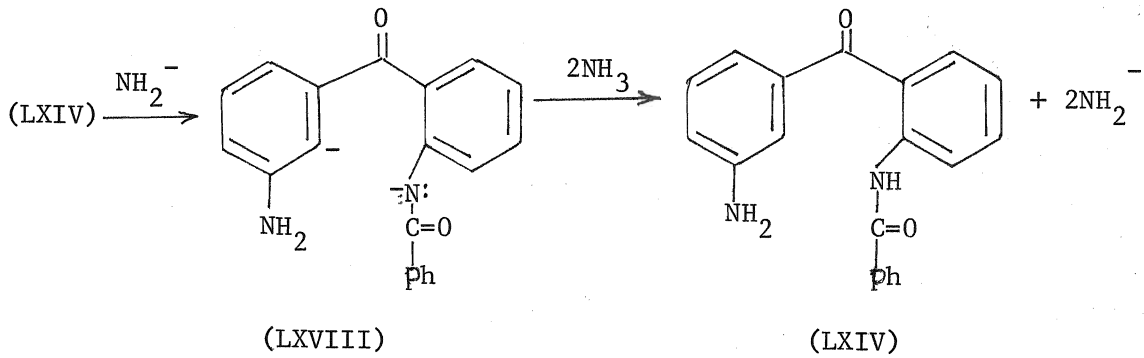
9-Acridone (LXV)			m.p.	yield	Reaction Solvent
R	R'	R''			
NO_2	H	Me	285-287°	82	DMF
Cl	H	ToS	172	40	$EtOC_2H_4OH$

Of these products, N-benzoylacridone is presumably formed by internal capture of the aryne by the nitrogen of the original benzamido-group. It is not known whether the ketonic carbonyl group

is present at this stage or has added amide ion. It is interesting that the N-benzoyl group is not cleaved under the reaction conditions.



The second product, considered to be 3-amino-2'-benzamido-benzophenone, is the result of capture of intermediate aryne by external addition of amide ion.

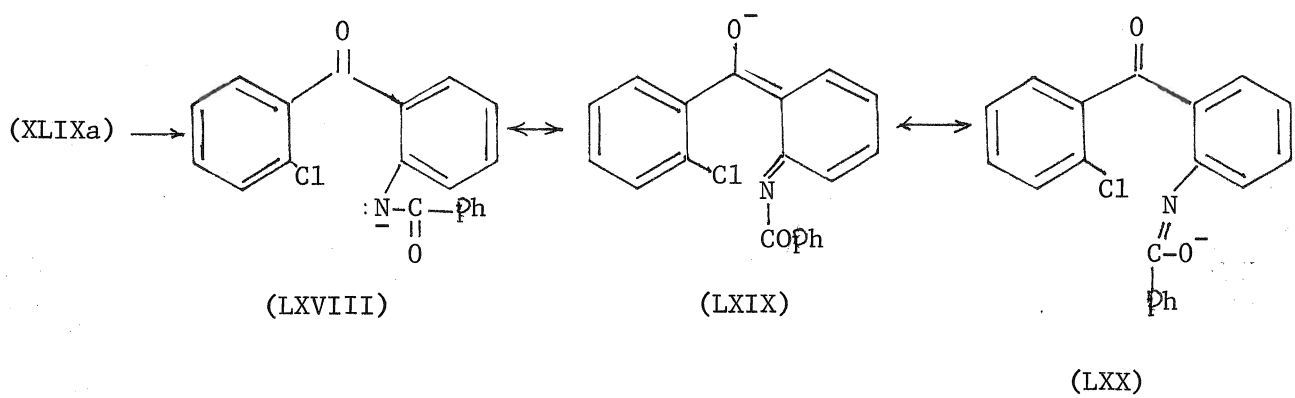


(ii) (b) <u>The Action of Potassium Amide on 2-Benzamido-2'-chlorobenzophenone</u>

Bunnett and Hrutfiord[17] have shown that 2-chlorobenzophenone undergoes the Haller-Bauer scission when treated with potassium amide in liquid ammonia. 2-Chlorobenzophenone has a carbonyl group which is

very susceptible to nucleophilic attack because of the halogen atom which decreases the electron density at the ketonic carbon atom. Thus scission should be prevented, or at least reduced, when there is an extra substituent which increases the electron density at the sensitive carbon atom.

An N-benzoyl group would be an ideal substituent for this purpose, as it would lose a proton in a basic solution, to give a benzoylimide anion, which would increase the electron density at the carbonyl carbon; canonical forms, such as (LXVIII) to (LXX) indicate this.

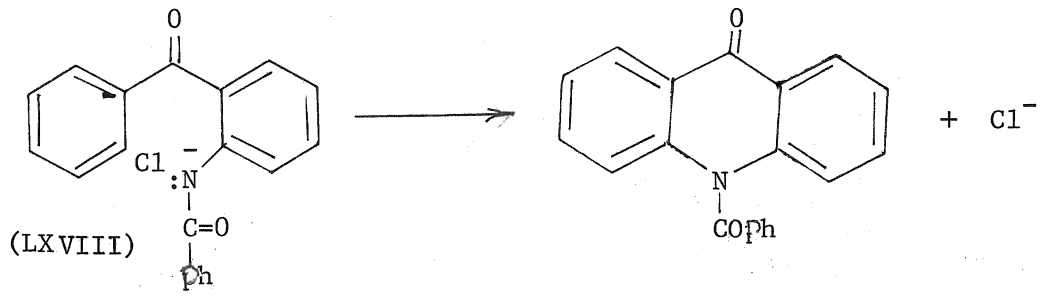


2-Benzamido-2'-chlorobenzophenone (XLIXa) was added in ethereal solution to potassium amide in liquid ammonia, dried <u>in situ</u> (see experimental). After four hours, excess potassium amide was decomposed by adding ammonium chloride, and the organic products were isolated using ether and 2N hydrochloric acid. The acidic solution was made alkaline when a small amount of material (2.5%) possibly starting material (t.l.c.), separated. The ethereal solution was extracted with aqueous sodium hydroxide solution, but acidification of the basic solution and evaporation gave only inorganic salts.

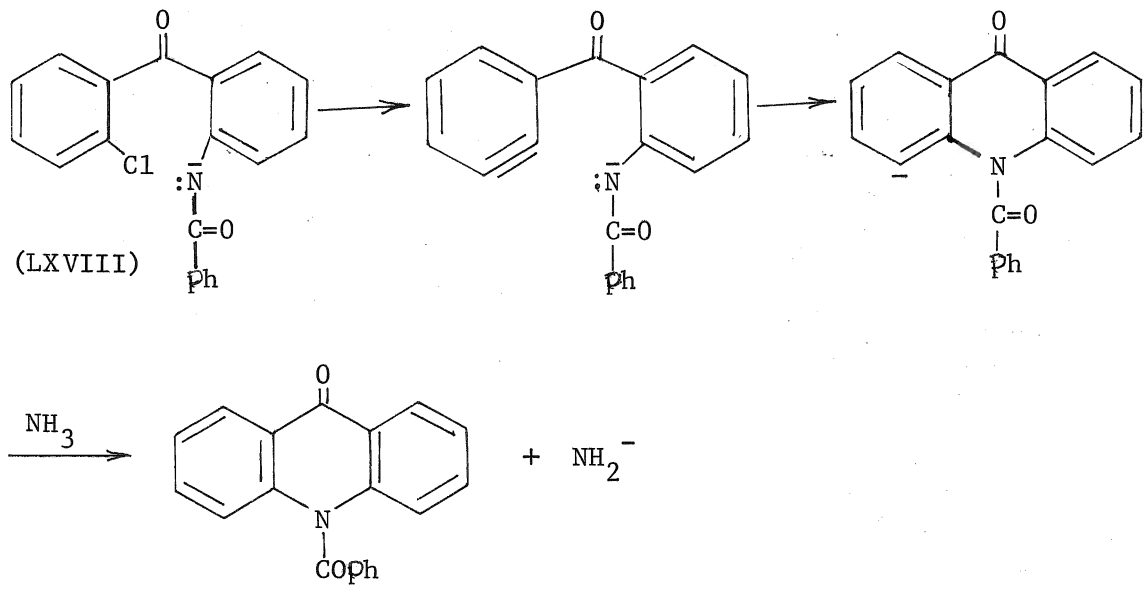
The residual ethereal layer was dried, evaporated, and the residue was crystallized from hexane giving N-benzoylacridone, m.p. 198-200°. The yield was 66% and the product was identical (mixed m.p., i.r., U.V., n.m.r. and mass spectra) with N-benzoylacridone prepared by the alternative synthesis described above.

The formation of N-benzoylacridone in this reaction may involve an intramolecular nucleophilic substitution mechanism in addition to the aryne mechanism discussed in the previous case of 2-benzamido-3'-chlorobenzophenone. (See page 35)

(i) Intramolecular nucleophilic substitution:



(ii) The aryne mechanism:



Attempted Reaction 2-Amino-2'- and 3'-chlorobenzophenones with Potassium Amide in Liquid Ammonia

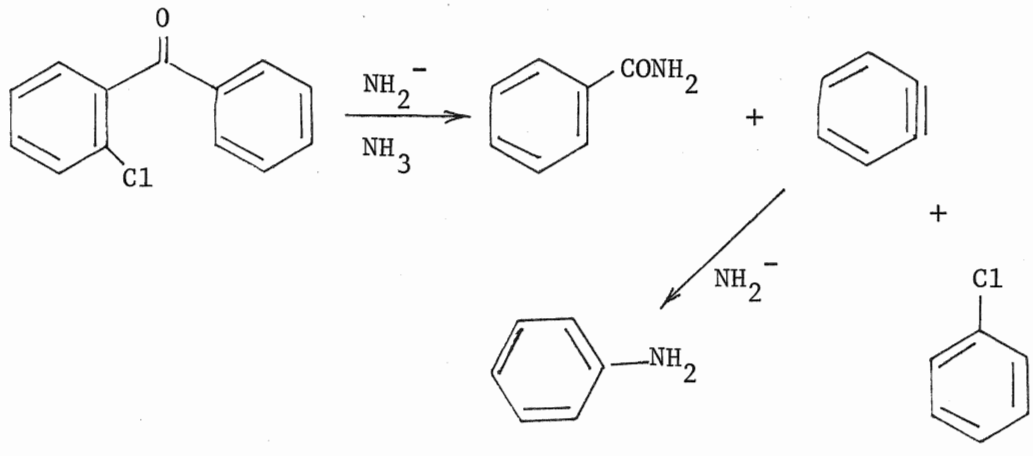
Attempts were made to convert the above two ketones to acridone by reaction with potassium amide in liquid ammonia, but without success; 2-amino-2'-chlorobenzophenone was recovered in 91% yield and 2-amino-3'-chlorobenzophenone was recovered in 78% yield. The reasons for failure of reaction are not clear, but possibly insoluble potassium anilates were formed and reaction was prevented. After completion of the main thesis work, different conditions were established for converting both ketones to acridone. These reactions are described in the Appendix.

CONCLUSIONS:

N-Benzoylacridones can thus in principle be prepared from a variety of halogenobenzophenones, under conditions that will not affect the N-benzoyl group. This would seem to be a useful new approach to syntheses of acridones since the procedure involves basic conditions and low temperatures. A further useful feature is that N-benzoyl derivatives can be made in this way, since direct benzoylation of acridone is reported to give O-benzoylacridine[43]. A modified synthesis involving higher temperatures, but still employing basic conditions, has been developed for acridones bearing no N-substituent. (See Appendix)

SECTION II

There are formally certain possibilities for heterocyclic synthsis which could take advantage of Haller-Bauer scission under the conditions employed by Bunnett and Hrutfiord for scission of o-chlorobenzophenone[17].



Two cases which were examined in the present work were 1-chlorofluorenone and 1-chloroanthraquinone.

(i) <u>1-Chlorofluorenone</u>

For 1-chlorofluorenone, several possible reaction pathways exist for reaction with potassium amide in ammonia.

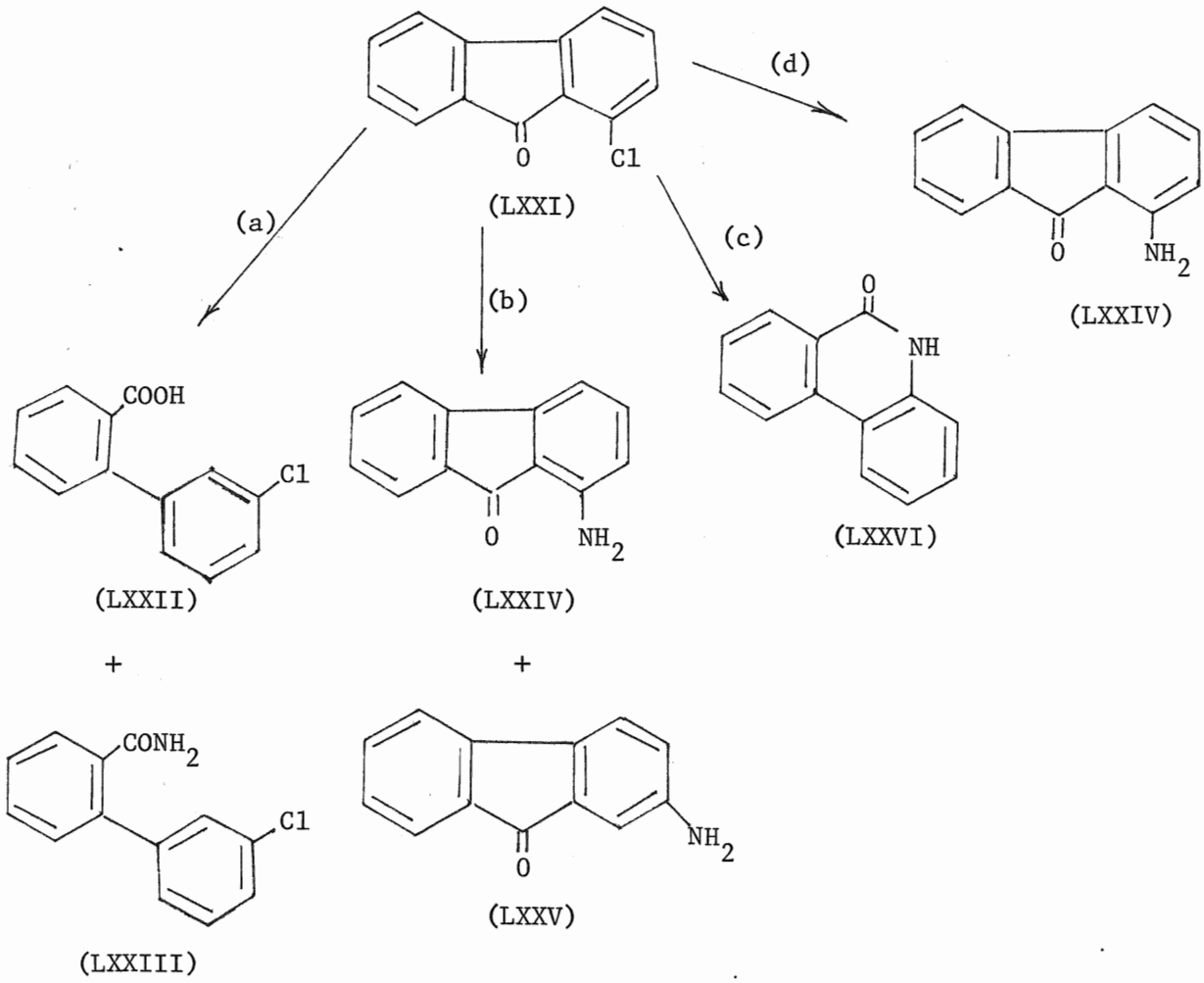
(a) If the reaction involves scission, 3-chlorobiphenyl-2'-carboxylic acid and its amide would be formed.

(b) If the reaction involves formation of aryne without scission, the formation of 1-aminofluorenone and 2-aminofluorenone would be expected.

(c) If the reaction involves scission and aryne formation, followed by intramolecular capture of the intermediate aryne, the formation of 9-phenanthridone would be expected.

(d) If the reaction proceeds by direct nucleophilic substitution, 1-aminofluorenone would be formed.

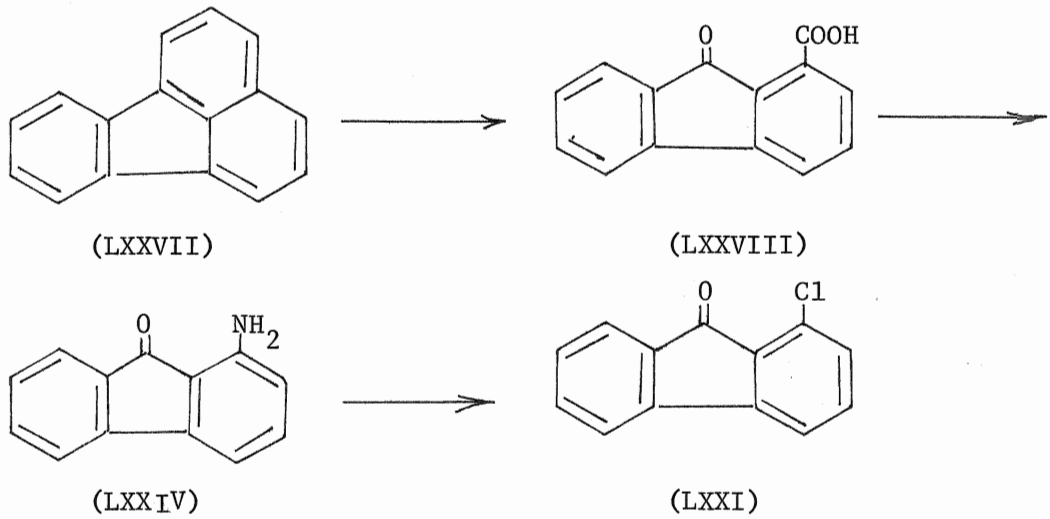
These possibilities are summarized in scheme 7, though it was recognized that (LXXII) and (LXXIII) might proceed further to arynes and derived products.



scheme 7

Preparation of 1-Chlorofluorenone

1-Chlorofluorenone was prepared from fluoranthene (LXXVII) by the following route:



Oxidation of fluoranthene with chromic acid in glacialacetic acid solution using Fieser and Seligman's procedure[44] gave fluorenone-1-carboxylic acid in 56% yield. The acid crystallized satisfactorily from isopropanol, and spectroscopic data were consistent with structure (LXXVIII).

Fluorenone-1-carboxylic acid (LXXVIII) was successfully converted by application of the Curtius reaction to 1-aminofluorenone (LXXV), which was obtained in 33% yield. An attempt using the Schmidt reaction was unsuccessful.

Bell and Gibson[45] had reported a similar preparation of 1-aminofluorenone using the Curtius reaction, but the yield was 27% only.

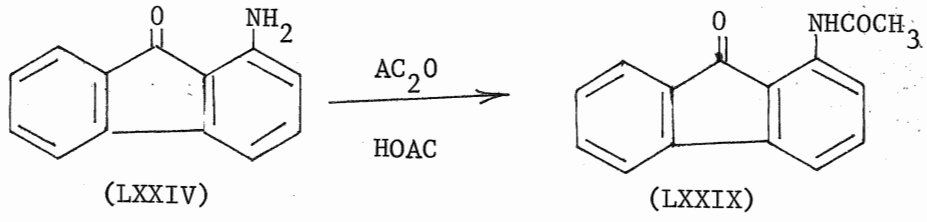
1-Aminofluorenone was treated with sodium nitrite in acid solution keeping the temperature between 0-5°. The diazonium salt was poured into cuprous chloride solution to give the crude product. Crystallization from aqueous ethanol gave pure 1-chloro-fluorenone as yellow plates in 50% yield. An attempted preparation by the Bell-Gibson's procedure was unsuccessful, although the properties of ~~their~~ compound were the same as those of 1-chlorofluorenone prepared in the present work. Spectroscopic properties are in agreement with the assigned formula.

Treatment of 1-Chlorofluorenone with Potassium Amide in Liquid Ammonia

1-Chlorofluorenone was added in dry tetrahydrofuran solution to potassium amide in liquid ammonia, dried *in situ* (see experimental) After four hours, excess potassium amide was decomposed by adding ammonium chloride and the organic products were isolated using ether and water. The aqueous solution (basic) was acidified with hydrochloric acid, and evaporated *in vacuo* to give slightly impure ammonium chloride. That there may have been slight scission of 1-chlorofluorenone during the reaction was indicated by the mass spectrum of the ammonium chloride fraction which showed m/e = 234 (37%) [M^+, ^{37}Cl], and 232 (90%) [M^+, ^{35}Cl], corresponding to the parent ion for 3-chloro-biphenyl-2-carboxylic acid. The residual ethereal extract, thought to contain neutral and basic materials, was dried and evaporated. The residue contained four different compounds (t. l. c.). Separation

on Florisil gave 1-chlorofluorenone (32%), 1-aminofluorenone in 46% yield (calculated on the basis of consumed starting material), and two unidentified compounds. The two unidentified compounds were submitted to acetylation conditions shown in a separate experiment to be satisfactory for acetylating 1-aminofluorenone. The two compounds were unaffected though the reaction mixture was seen to contain a trace of 1-acetylaminofluorenone. It was inferred, therefore, that neither of the two compounds was 2-aminofluorenone. The amount of this mixture was small and neither compound was identified.

1-Acetylaminofluorenone (LXXIX) was prepared as a reference sample by heating a mixture of glacial acetic acid, acetic anhydride and 1-aminofluorenone (LXXIV). This yield was 82%, m.p. 134-136.5^{o}.



CONCLUSION:

1-Aminofluorenone was the main product formed by treatment of 1-chlorofluorenone with potassium amide in liquid ammonia. This compound might be formed by either aryne or substitution mechanisms.

(ii) 1-Chloroanthraquinone

For 1-chloroanthraquinone, several possible reaction pathways exist for reaction with potassium amide in liquid ammonia.

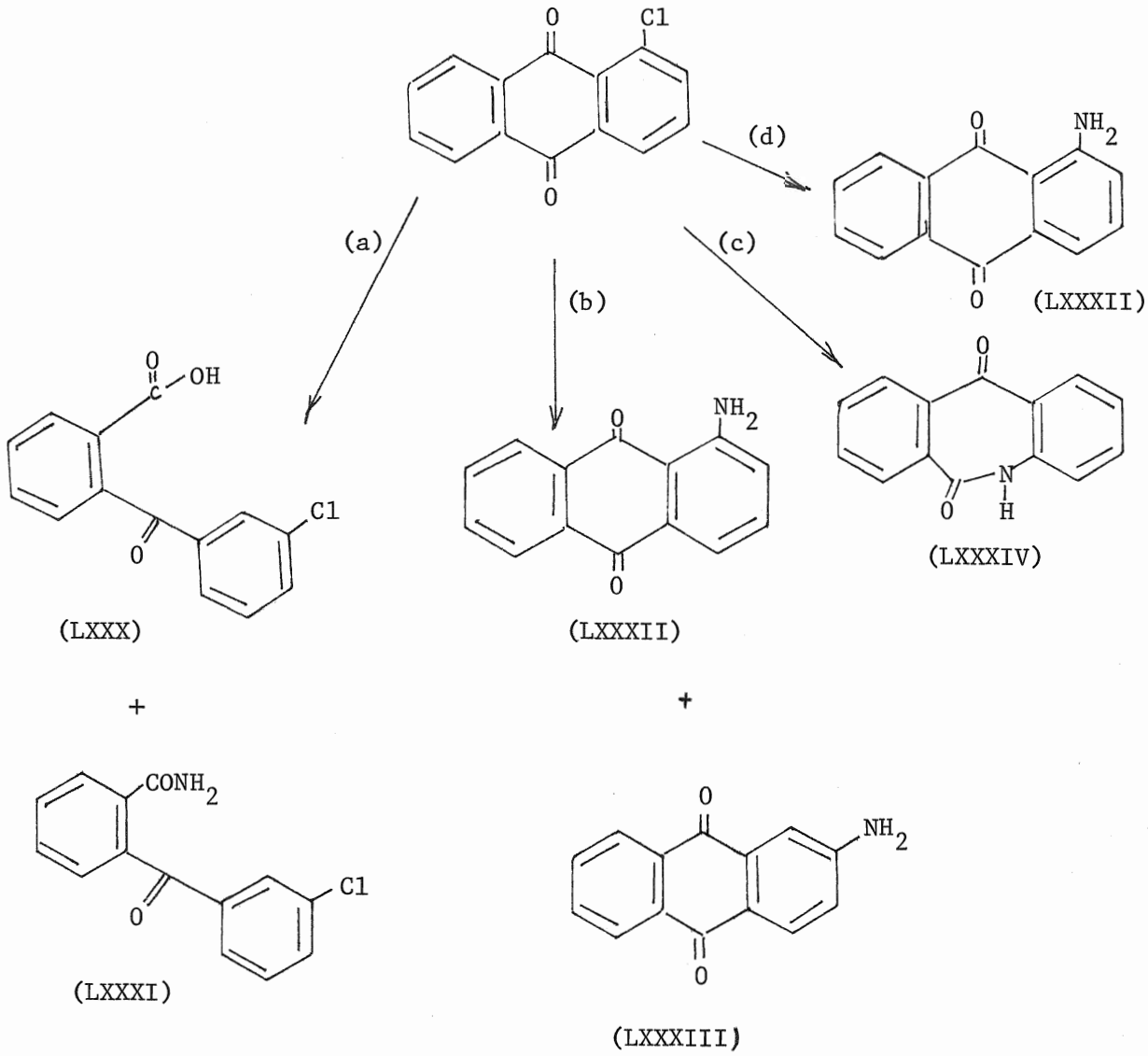
(a) If the reaction involves scission, 3-chlorobenzophenone-2'-carboxylic acid (LXXX) and its amide (LXXXI) would be formed.

(b) If the reaction involves formation of aryne without scission, the formation of 1-aminoanthraquinone (LXXXII) and 2-aminoanthraquinone (LXXXIII) would be expected.

(c) If the reaction involves scission and aryne formation, followed by intramolecular capture of the intermediate aryne, the formation of (LXXXIV) would be expected.

(d) If the reaction proceeds by direct nucleophilic substitution, 1-aminoanthraquinone (LXXXII) would be formed.

These possibilities are summarized in scheme 8, though it was recognized that (LXXXII) and (LXXXIII) might proceed further to arynes and derived products.


O
Cl
O
(a)
(b)
(c)
(d)
O
NH2
O
(LXXXII)
O
OH
Cl
O
(LXXX)
O
NH2
O
(LXXXII)
O
N
H
O
(LXXXIV)
+
+
CONH2
Cl
O
(LXXXI)
O
NH2
O
(LXXXIII)

scheme 8

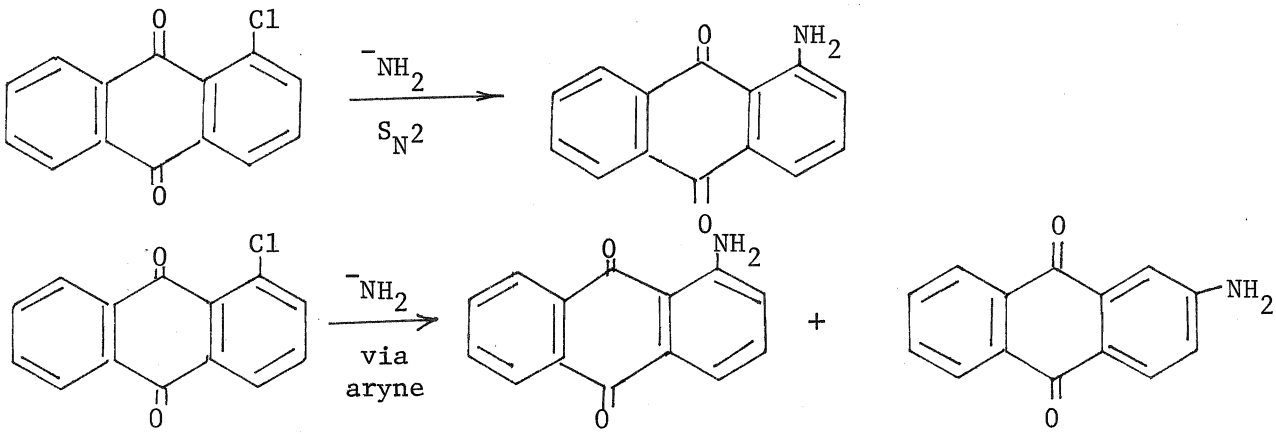
1-Chloroanthraquinone, in dry tetrahydrofuran solution, was treated with potassium amide in liquid ammonia, dried *in situ*. After four hours, ammonium chloride was added, and the liquid ammonia was allowed to evaporate. The residue was extracted with water and chloroform. The aqueous solution was acidified and evaporated *in vacuo* to give ammonium chloride and potassium chloride. Evidently there was no scission of 1-chloroanthraquinone possibly due to greater steric hindrance at the carbonyl group than at the 1- and 2- positions. The residual chloroform solution was extracted with hydrochloric acid; the acid solution was made alkaline and so provided a small amount of 1-aminoanthraquinone and 2-aminoanthraquinone. The remaining chloroform solution, thought to contain only neutral material was made alkaline, dried and evaporated. The residue was crystallized and was found to contain at least four compounds. Separation on alumina, using chloroform as eluant gave 1-chloroanthraquinone (12%), 1-aminoanthraquinone (49%), 2-aminoanthraquinone (25%), and two unidentified compounds (17%).

1-Aminoanthraquinone and 2-aminoanthraquinone were thus found in the "neutral fraction", presumbably because of low basicity.

1-Aminoanthraquinone and 2-aminoanthraquinone were identified in each case by m.p. and spectroscopic comparisons, (i.r., mass, and u.v. spectra).

The formation of 1-aminoanthraquinone in this reaction may involve an intermolecular nucleophilic substitution mechanism in addition

to the aryne mechanism, but the formation of 2-aminoanthraquinone involves only an aryne mechanism, (cine-substitution).



(iii) Attempted Reaction 2-Chloroanthraquinone Treatment with Potassium Amide in Liquid Ammonia

It was of interest to determine how 2-chloroanthraquinone would behave when treated with potassium amide in liquid ammonia under the usual conditions. In fact, little reaction was observed, and starting material was recovered in 82% yield. It is not clear at this stage whether the compound is unreactive or the conditions, e.g. solubility, are not suitable for reaction.

CONCLUSIONS:

1-Aminoanthraquinone and 2-aminoanthraquinone are the main products of reaction of 1-chloroanthraquinone with potassium amide in liquid ammonia; apparently no scission occurs. The second amine indicates an aryne mechanism. The first amine may be formed through aryne or nucleophilic substitution mechanisms.

EXPERIMENTAL

INSTRUMENTATION AND TECHNIQUES

1. Melting Point

These were measured on an "Electrothermal" m.p. apparatus.

2. Thin Layer Chromatography

Silica Gel 254 supported on pre-prepared aluminum sheets (supplied by E. Merck, Darmstadt, Germany) were used.

3. Infra-red Spectra

Compounds were mixed with potassium bromide and compressed into thin disks, from which spectra were obtained on a "Perkin Elmer (model 237 B)" grating infra-red spectrophotometer.

4. Nuclear Magnetic Resonance Spectra

The solvents used are indicated in the text. The spectra were obtained on a "Varian A 60" nuclear magnetic resonance spectrometer.

5. Mass Spectra

The machine used to obtain these spectra was an A. E. I. - MS30, double beam, double focusing mass spectrometer.

6. Ultra-violet Spectra

The solvents used are indicated in the text. The spectra were obtained on a "Cary - 14 recording spectrophotometer".

7. Yield

For syntheses of benzophenones, yields are based on material used for the reaction. For potassium amide-liquid ammonia reactions, yields are calculated in terms of unrecovered starting materials.

8. Ozonator

(a) Apparatus

A Welsbach Model T-408 Laboratory Ozonator, which is designed for operation on a 115 volts, 60 cycle circuit was used for all the ozonization experiments.

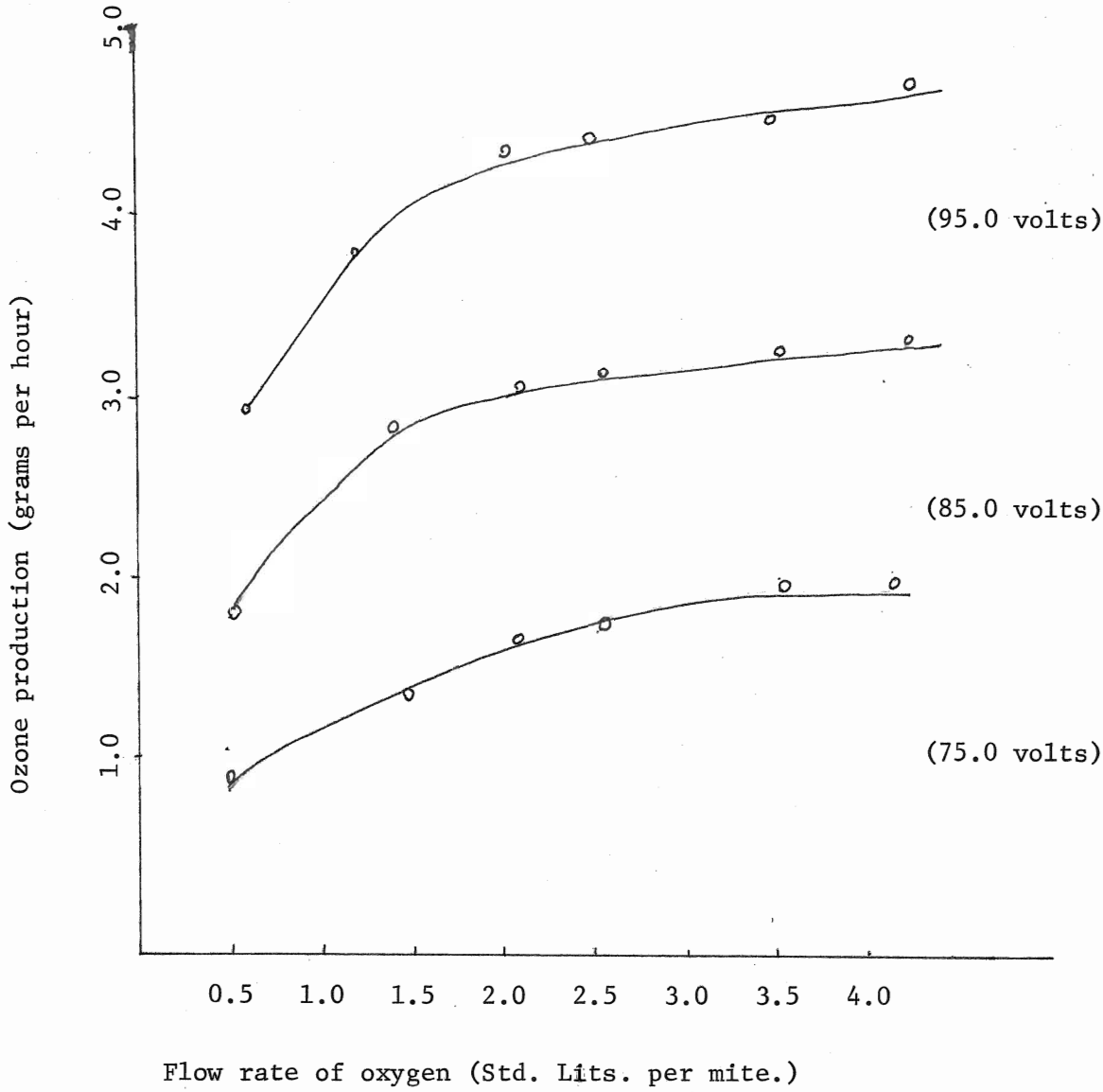
(b) Procedure

Ozone concentration was determined by passing a measured amount of ozonized gas through a 2% solution of neutral potassium iodide. This was done by keeping the flow meter reading constant and passing the ozonized gas for five minutes through the potassium iodide solution, maintaining the operating pressure and voltage constant. The resulting solution was acidified with 1 M sulfuric acid and the liberated iodine was titrated with 0.1 M sodium thiosulphate solution.

Ozone reacts with neutral potassium iodide solution according to the equation:

$$O_3 + H_2O + 2KI \longrightarrow O_2 + I_2 + 2KOH$$

The curve plotted with oxygen flow rate in standard litres per minute (SLPM) against grams of ozone generated per hour gave a fairly accurate idea about the conditions to be maintained for the production of ozone at a particular rate.



Preparation of Potassium Amide in Liquid Ammonia

1. Using liquid ammonia dried in situ

Commercial liquid ammonia was introduced into a 1 l. 3-necked flask, fitted with a dry-ice condensor, and a mechanical stirrer. Small chips of potassium were added, until the mixture became permanently blue. A small crystal of ferric nitrate was added, followed by the requisite amount of potassium. The mixture was then stirred, until the intense blue colour faded.

2. Using redistilled liquid ammonia

Commercial liquid ammonia was introduced into a 1 l. 3-necked flask. Small chips of sodium were added, until the mixture attained a permanent blue colouration. A water bath was used to drive off the ammonia into a second 3-necked flask, fitted with a cold dry-ice condensor, a mechanical stirrer, and if solids had to be added a right angled glass tube, so the solid could be added without opening the system.

The ammonia was condensed with solid carbon dioxide in acetone. A small chip of potassium was added. This always turned the mixture deep blue. A small crystal of ferric nitrate was added followed by the requisite amount of potassium. The mixture was then stirred until the blue colour gave way to the grey of potassium amide.

SECTION I

(i) Intermediates: ω-(o-Chlorophenyl)acetophenone

A mixture of o-chlorophenylacetic acid (30.0 g., 0.176 mole) and thionyl chloride (50 ml., 0.83 mole) was refluxed for 1 hour. The excess of thionyl chloride was then distilled off under reduced pressure (15 mm.), last traces being removed by co-distillation with benzene (50 ml.). The acid chloride was then diluted with dry benzene (150 ml.) and transferred to a 500 ml. three-necked flask, equipped a mechanical stirrer and a thermometer. Dry powdered aluminium chloride (21 g., 0.158 mole) was added slowly, keeping the temperature between 0° and 10^{0} by means of an ice-bath. Then the reaction mixture was refluxed for 1

hour. The resultant suspension was poured into a stirred mixture of cracked ice (200 g.) and concentrated hydrochloric acid (60 ml.). The mixture was extracted with a benzene-ether mixture (3 x 50 ml.)(1:1). The organic layers were combined, washed with water (3 x 50 ml.), dried over anhydrous magnesium sulphate, and filtered. The solvent was removed under reduced pressure (15 mm.) and the residue, which solidified on cooling (m.p. 62-68°), was crystallized from light petroleum (b.p. 30-60°) to give pure ω-(o-chlorophenyl)acetophenone (31 g., 77%) as colourless plates, m.p. 69° (lit.,[34] m.p. 70.5°). The i.r. spectrum showed νmax. 1663 (>C = 0), 1600, 1430, 1313, 1205, 775, 748 cm^{-1}. The mass spectrum showed, at 70 e.v., m/e = 232 (0.006) (M^+, ^{37}Cl), 231(0.005) 230(0.007) (M^+, ^{35}Cl), 196(0.58), 195(33), 165(1.7), 127(2.1), 126(0.97), 125(7.2), 106(8.2), 105(100%), 99(2.5) 91(1.5), 90(3.0), 89(9.9), 78(4.5), 77(49.), 76(4.7), 75(2.1), 74(4.3), 73(1.8), 63(8.5), 51(30), 50(11), and at 24 e.v., m/e = 232 (0.013) (M^+, ^{37}Cl), 231(0.018), 230(0.036) (M^+, ^{35}Cl), 196(3.2), 195(22), 166(2.8), 165(9.0), 127(7.2), 126(2.8), 125(24), 107(2.9), 106(21), 105(100%), 101(2.6), 99(8.1), 91(4.1), 90(8.3), 89(33), 78(19), 77(66.), 76(9.0), 75(3.7), 74(4.8), 73(4.2), 65(3.4), 64(3.2), 63(23), 62(3.5), 51(3.8), 50(18). ^{1}Hn.m.r (CCl_4): 4.3 δ(singlet; 2H), 7.2-7.5 δ(multiplet; 5H), 7.9-8.1 δ(multiplet; 4H).

<u>ω-(m-Chlorophenyl)acetophenone</u>

This was made by the literature method and had m.p. 39-41° (lit.,[35] m.p. 43°). The i.r. spectrum showed ν max., 1675(>C=0), 1595, 1574, 1468, 1215, 996, 755, 675 cm^{-1}. The mass spectrum showed, at 70 e.v.,

m/e = 232 (0.004) (M^+, ^{37}Cl), 231(0.003), 230(0.011) (M^+, ^{35}Cl), 166(0.53), 127(1.4), 125(3.9), 106(10), 105(100%), 92(4.0), 77(81), 76(3.9), 63(7.1), 62(4.0), 51(67), 43(3.2), 39(5.0), and at 24 e.v., m/e = 232 (0.28) (M^+, ^{37}Cl), 231(0.15), 230(0.40) (M^+, ^{35}Cl), 166(1.6), 127(4.5), 125(16), 106(20), 105(100%), 91(2.1), 90(7.4), 77(32), 76(3.8), 75(3.5), 63(9.3), 62(2.0), 51(38), 43(0.02), 39(4.7). ^1H n.m.r. (CS_2): 4.15 δ (singlet; 2H), 7.14-7.58 δ (multiplet; 7H), 7,83-8.01 δ (multiplet; 2H).

2-Phenyl-3-(o-chlorophenyl)indole

A mixture of ω-(o-chlorophenyl)acetophenone (9.5 g., 0.041 mole) and phenylhydrazine (4.5 g., 0.042 mole) was heated on the steam bath for 4 hours. The crude phenylhydrazone was cyclized by refluxing the oil thus obtained in a mixture of concentrated hydrochloric acid (50 ml.) and methanol (75 ml.) for 48 hours. The methanol-hydrochloric acid mixture was decanted from the precipitate which formed. This solid residue was dissolved in methylene chloride (60 ml.) and the solution was washed with an excess of dilute ammonia (1:1) (3 x 30 ml.), (ammonia, s.g. 0.90). The methylene chloride layer was then washed well with water (3 x 50 ml.), dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure (15 mm.). The brown residual crude product was crystallized from benzene-light petroleum (b.P. 115-120°) to give a crystalline, but still impure, product. Separation by column chromatography on Florisil using benzene-light petroleum (b.P. 115-120°) mixture (1:1) as eluant gave pure 2-phenyl-3-(o-chlorophenyl)indole (7.6 g., 70%) as white plates, m.p. 146-148°

(Found: C, 78.98; H, 4.80; Cl, 11.85. $C_{20}H_{14}ClN$ requires C, 79.07; H, 4.64; Cl, 11.67%). The i.r. spectrum showed ν max. 3380(NH), 1598(ω), 1449, 1052, 753, 745(S), 678 cm^{-1}. The mass spectrum showed m/e = 306 (4.1), 305(12.)(M^+, ^{37}Cl), 304(7.0), 303(35) (M^+, ^{35}Cl), 268(9.5), 267(14.), 186(6.2), 165(5.1), 135(10.), 134.5(4.1), 134(4.1), 77(4.8), 76(5.2), 103(6.4), 57(36.), 42(40), 41(100%). ^1H n.m.r. (CCl_4): 8.1 δ (broad singlet; 1H) (exchangable with D_2O); 7.10-7.30 δ (multiplet; 13H).

2-Phenyl-3-(m-chlorophenyl)indole

A mixture of ω-(m-chlorophenyl)acetophenone (23 g., 0.100 mole), and phenylhydrazine (12 g., 0.111 mole) was heated on the steam bath for 4 hours. The crude phenylhydrazone was cyclized by refluxing the oil thus obtained in a mixture of concentrated hydrochloric acid (166 ml.) and methanol (250 ml.) for 48 hours. Methanol was removed under reduced pressure (15 mm.), and then aqueous solution was removed *in vacuo*. The solid residue was dissolved in methylene chloride (250 ml.) and the solution was washed with an excess of dilute ammonia (1:1) (ammonium hydroxide, s.g. 0.90) (3 x 30 ml.). The methylene chloride layer was then washed well with water (3 x 50 ml.), dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure (15 mm.). The brown residual crude product was crystallized from acetone-light petroleum (b.P. 30-60°) mixture (1:3) using dry ice bath cooling to give a crystalline, but still impure, product (15 g.). Separation by column chromatography on Florisil using benzene-light petroleum (b.P. 60-90°) mixture (1:1) as eluant gave a light yellow

product. Crystallization from hexane gave pure 2-phenyl-3-(m-chlorophenyl)indole (14.5 g., 49%) as white plates, m.p. 114-115° (Found: C, 78.80; H, 4.57; Cl, 11.8. $C_{20}H_{14}ClN$ requires C, 79.07; H, 4.64; Cl, 11.67%). The i.r. spectrum shows ν max. 3400(S)(N-H), 1595, 1450, 1435, 1250, 865, 775(S), 743(S), 698 cm^{-1}. The mass spectrum showed m/e = 306(70%), 305(33%), (M^+, ^{37}Cl), 304(23%), 303(100%) (M^+, ^{35}Cl), 268(14%), 267(35%), 266(7.0%), 166(3.0%), 165(17%), 164(4.7%), 163(7.0%), 134(12.%), 133.5(16.%), 133(12%), 77(4.2%), 76(5.2%), 42(39.%), 61(92.0%). 'H n.m.r. ($CDCl_3$): 7.85 δ (broad singlet; 1H) (exchangable with D_2O), 7.7-7.8δ (multiplet; 13H).

2-Benzamido-2'-chlorobenzophenone

A solution of 2-phenyl-3-(o-chlorophenyl)indole (10 g., 0.030 mole) in glacial acetic acid (150 ml.) was ozonized to completion using ozone (2.21 g., 0.064 mole); 50% more than the theoretical amount of ozone was passed at a flow rate of 1.5 g/hour. After 1½ hours the passage of ozone was stopped. Then the solution was poured into water (150 ml.) with stirring. The solution was allowed to stand for 2 hours and then extracted with methylene chloride (3 x 50 ml.). The methylene chloride solution was washed with a saturated solution of sodium carbonate (3 x 50 ml.), followed by water (3 x 50 ml.), dried over anhydrous magnesium sulphate and filtered. The methylene chloride was removed under reduced pressure (15 mm.) leaving an oily residue (5.4 g.). Separation by column chromatography on Florisil using hexane as eluant gave pure 2-benzamido-2'-chlorobenzophenone (4.0 g., 36.%) as yellow plates, m.p. 109-110°. (Found: C, 71.56; H, 4.07; N, 4.08.

$C_{20}H_{14}ClNO_2$ requires C, 71.50; H, 4.20; N, 4.20%). The i.r. spectrum showed νmax. 3200(N-H), 1750(>C = 0), 1650(NHCO), 1575, 1525, 1448, 1276, 1251, 1249, 875(ω), (overtone of >C = 0), 750, 698 cm^{-1}. The mass spectrum showed m/e = 353(0.27) [$M^+(C_{20}H_{14}ClNO_3)$, ^{37}Cl], 351(0.81) [$M^+(C_{20}H_{14}ClNO_3)$, ^{35}Cl], 337(18) [M^+, ^{37}Cl], 336(13), 335(54), [M^+, ^{35}Cl] 245(1.7), 233(1.5) 232(3.5), 231(6.2), 230(10.), 229(8.1), 197(27.), 196(81.), 195(23), 152(4.6), 151(2.3), 112(3.5), 111(27), 106(58.), 105(100), 104(3.1), 78(2.7), 77(81), 76(15), 74(4.2). ^1H n.m.r. (CS_2): 5.10-5.40 δ (multiplet; 2H), 5.50-5.89 δ (multiplet; 9H, 6.25-6.45 δ (multiplet; 2H), 7.21-7.45 δ (doublet; 1H).

2-Benzamido-3'-chlorobenzophenone

A solution of 2-phenyl-3-(m-chlorophenyl)indole (7.2 g., 0.023 mole) in glacial acetic acid (150 ml.) was ozonized to completion using ozone (2.21 g., 0.046 mole); 50% more than the theoretical amount of ozone was passed at a flow rate of 1.5 g./hour. After 1½ hours, the passage of ozone was stopped. Then the solution was poured into water (150ml.) with stirring. The solution was allowed to stand for 2 hours, and then extracted with methylene chloride (3 x 50 ml.). The methylene chloride solution was washed with a saturated solution of sodium carbonate (3 x 50 ml.), followed by water (3 x 50 ml.), dried over anhydrous magnesium sulphate and filtered. The methylene chloride was removed under reduced pressure leaving an oily residue (4.1 g.). Separation by column chromatography on Florisil using hexane as eluant gave pure 2-benzamido-3'-chlorobenzophenone (3.2 g., 42%) as yellow plates, m.p. 123-124.5°. (Found: C, 71.32; H, 4.30; N, 4.47.

$C_{20}H_{14}ClNO_2$ requires C, 71.50; H, 4.20; N, 4.20%). The i.r. spectrum shows ν max. 3200 (>N-H), 1665(>C=O), 1651(NH-C=O), 1601, 1590, 1578, 1450, 1250, 750, 700 cm^{-1}. The mass spectrum showed m/e = 337 (3.1) (M^+, ^{37}Cl), 336(2.0), 335(8.6) (M^+, ^{35}Cl), 232(0.57), 231(0.86), 230(2.0), 197(3.1), 196(17.), 195(2.6), 139(2.0), 106(10), 105(100%), 78(8.0), 77(86), 76(5.1), 75(9.7), 74(4.6), 51(44.), 36(11.), 28(34.).

2-Amino-2'-chlorobenzophenone

A solution of 2-benzamido-2'-chlorobenzophenone (1.4 g., 0.0041 mole) in boiling ethanol (30 ml.) was added to a solution of sodium hydroxide (7.5 g.) in water (10 ml.). The mixture was refluxed for 4 hours, diluted with water (120 ml.) and concentrated to ca. 85 ml. under reduced pressure (15 mm.). The resulting mixture was poured into cold water (150 ml.) when crude 2-amino-2'-chlorobenzophenone solidified. The solid was filtered off, washed with cold water and dried in vacuo overnight. The crude solid was extracted with benzene (5 x 30 ml.) and the solution was evaporated under reduced pressure (15 mm.) leaving an oil which crystallized from acetone (10 ml.) and hexane (10 ml.) mixture to give pure 2-amino-2'-chlorobenzophenone (0.45 g., 40%) as pale yellow plates, m.p. 58-60° (lit.,[41] m.p. 58°). The i.r. spectrum showed ν max. 3400 (>N-H), 1625(>C=O), 1530, 1300, 754, 735 cm^{-1}. The mass spectrum showed m/e = 234 (0.71), 233(3.8) (M^+, ^{37}Cl), 232(3.3), 231(14.) (M^+, ^{35}Cl), 230(6.7) (M^+ -1), 215(1.3), 198(0.38), 197(3.8), 196(25.) (M^+ -Cl), 195(3.3), 167(3.1), 141(1.9), 139(6.7), 123(7.1), 122(100%), 120(16.), 113(1.9), 111(4.3), 106(7.6), 105(60.), 104(1.4), 93(2.4), 92(1.2), 91(9.6), 77(7.4), 76(76.), 75(6.0), 74(6.2), 73(6.4).

2-Amino-3'-chlorobenzophenone

A solution of 2-benzamido-3'-chlorobenzophenone (4.6 g., 0.0137 mole) in boiling ethanol (40 ml.) was added to a solution of sodium hydroxide (15 g.) in water (20 ml.). The mixture was refluxed for 4 hours on a steam bath, then diluted with water (120 ml.) and concentrated under reduced pressure (15 mm.). The residue was poured into cold water (150 ml.) and the crude brown solid was extracted with benzene (3 x 50 ml.). The benzene solution was washed with water (3 x 50 ml.), then dried over anydrous magnesium sulphate and the solvent was removed under reduced pressure (15 mm.) leaving an orange liquid. A mixture of acetone (20 ml.) and hexane (20 ml.) was added and the solution was chilled in a dry-ice bath when the crude product crystallized. Crystallization from hexane gave a yellow solid (2.4 g.) which showed three spots on t.l.c. (chloroform). Separation by column chromatography on Silica Gel (mesh 100-200) using benzene as eluant gave a yellow solid (2.1 g.) which crystallized from hexane to give pure 2-amino-3'-chlorobenzophenone (2.1 g., 66%) as yellow plates, m.p. 78-80°. (Found: C, 67.38; H, 4.28; N, 5.99. $C_{13}H_{10}ClNO$ requires C, 67.36; H, 4.39; N, 6.04%). The i.r. spectrum showed ν max. 3425($>$N-H stretching), 1615($>$C=0), 1540, 1301, 1248, 750 cm^{-1}. 'H n.m.r. (CCl_4): 6.20δ (broad singlet; 2H, exchangable with D_2O), between 6.6δ and 7.7δ (multiplet; 8H). The mass spectrum showed m/e = 233(28.) (M^+, ^{37}Cl), 232(38.), 231(76.) (M^+, ^{35}Cl), 230(100.) (M^+ -1), 196(54.), (M^+ -Cl), 167(16.), 134(24.), 120(11.), 111(32.), 92(165), 75(38.) 65(70.).

(ii) Reactions in Liquid Ammonia

(a) of 2-Benzamido-3'-chlorobenzophenone

2-Benzamido-3'-chlorobenzophenone (2 g., 0.006 mole) dissolved in anhydrous ether (60 ml.) was added to a solution of potassium amide, prepared from potassium (2 g., 0.051 mole) and liquid ammonia (200 ml.) dried *in situ*. The yellow-green mixture was stirred for 4 hours and ammonium chloride (5 g.) and ether (100 ml.) were then slowly added. The ammonia was allowed to evaporate overnight. A brown solid remained.

The residue was treated with 2N hydrochloric acid (3 x 50 ml.) and extracted with ether (5 x 50 ml.) to give ethereal solution (A) and an acid solution (B). The ethereal solution was extracted with 40% w/v sodium hydroxide solution (3 x 50 ml.) to give basic solution (C) and ethereal solution (D).

The acid solution (B) was made alkaline by 40% w/v sodium hydroxide when a crude yellow solid (0.37 g., 25%), m.p. 231-236° separated. Crystallization from n-propanol gave a pure yellow solid (0.32 g., 21%) (t.l.c.) m.p. 234-236°, which was not identified, but is thought to be 3-amino-2'-benzamidobenzophenone. The i.r. spectrum showed ν max. 3400 (>NH), 1677(>C=0), 1526, 1258, 750 cm^{-1}. The mass spectrum showed m/e = 318(0.86), 317(5.0), 316(24.)(M^{+}), 212(2.9), 211(19.), 210(3.3), 196(20.)(M^{+} - C_7H_6NO , 197(2.4), 195(4.3), 182(2.4), 181(1.9), 106(11.), 105(79.)(M^{+} - $C_{13}H_{10}NO$, 97(8.6), 96(2.9), 95(7.1), 77(100%), 65(9.5%).

The basic solution (C) was made acidic with 2N hydrochloric acid. The brown solid produced was filtered off, washed well with water (3 x 30 ml.), and dried to give a brown tarry solid (0.42 g.), m.p.

starting at 108° but not complete at 340°. The i.r. spectrum did not indicate any specific functional group.

Ethereal solution (D) was washed with water (50 ml.), dried over magnesium sulphate and evaporated to give a yellow solid (0.76 g., 42%), m.p. 194-198°; t.l.c. ($CHCl_3$) showed 3 spots. Separation by column chromatography on Florisil (mesh 100-200) using benzene as eluant gave, as main product, a brown solid, together with some tar (0.12 g.) which was not recovered.

The solid was crystallized from hexane to give pure N-benzoylacridone (0.64 g., 36%) as yellow plates, m.p. 198-199.5° (Found: C, 80.18; H, 4.62; N, 500. $C_{20}H_{13}NO_2$ requires C, 80.25; H, 4.37; N, 4.68%). The i.r. spectrum showed νmax. 3100 (>NH), 1649(>C=0), 1595, 1281, 750, 698 cm^{-1}. The mass spectrum showed m/e = 301(1.2%), 300(6.0), 299(25%)(M^+), 222(4.7), 196(2.5), 194(44), ($M^+ - C_7H_5\overset{+}{C}{\equiv}0$), 105(10.) ($M^+ - C_{13}H_8NO^+$), 77(13), 56(4.6), 51(5.8), 44(100%), 43(4.2), 41(4.6). The u.v. spectrum showed λmax. (MeOH) 210(logε = 4.01), 255(logε = 4.12) 408 mμ (logε = 3.37). ^{1}H n. m. r. ($CDCl_3$) 7.2-8.6δ (multiplet; 13H).

(b) of 2-Benzamido-2'-chlorobenzophenone

2-Benzamido-2'-chlorobenzophenone (2 g., 0.006 mole) dissolved in anhydrous ether (60 ml.) was added to a solution of potassium amide, prepared from potassium (2 g., 0.051 mole) and liquid ammonia (200 ml.) dried *in situ*. The green-yellow mixture was stirred for 4 hours and ammonium chloride (5 g.) and ether (50 ml.) were then slowly added. The ammonia was allowed to evaporate overnight. A brown solid remained.

The crude residue was treated with 2N hydrochloric acid (150 ml.) and extracted with ether (5 x 50 ml.) to give ethereal solution (A) and an acid solution (B). The ethereal solution was extracted with 40% (w/v) sodium hydroxide solution (3 x 50 ml.) to give a basic solution (C) and ethereal solution (D).

The acid solution (B) was made alkaline by 40%(w/v) sodium hydroxide to give a small amount of solid (0.051 g. 2.5%) which was apparently starting material (t.l.c.; ethyl acetate; R_f = 0.60).

The basic solution (C) was made acidic with 2N hydrochloric acid. This solution was evaporated in vacuo to give inorganic compounds. The i.r. spectrum did not indicate any specific functional group.

The ethereal solution (D) was washed with water (3 x 50 ml.), dried over anhydrous magnesium sulphate and evaporated leaving a yellow solid (1.42 g.), m.p. 193-196°. T.l.c. (chloroform) showed one main spot corresponding to N-benzoylacridone (R_f = 0.62, $CHCl_3$). The crude product was sublimed at 120°/15 mm. to give yellow plates (1.21 g., 67%), m.p. 198-200°. This compound was identified as N-benzoylacridone by mixed m.p. determinations with the previous sample (mixed m.p. 198-200°). The mass spectrum was identical with that of the previous sample of N-benzoylacridone. The u.v. spectrum showed similar absorptions, λ max. (MeOH): 210(logε = 4.00), 255(logε = 4.01), 408 mμ(logε = 3.31).

SECTION II

(i) 1-Chlorofluorenone Section

Fluorenone-1-carboxylic acid

Fluoranthene was oxidized to fluorenone-1-carboxylic acid substantially according to the directions of Fieser and Setigman (yield 56%, m.p. 191-193°). Crystallization from isopropanol gave long orange-red needles, m.p. 193-195^{o}(lit.,[44] m.p. 191-193°).

1-Aminofluorenone

This was prepared by a modification of the method used by Bell and Gibson[45].

Fluorenone-1-carboxylic acid (28 g., 0.144 mole) was refluxed with thionyl chloride (120 ml., 2.20 mole) for 2 hours on a steam bath. The excess of thionyl chloride was then distilled off under reduced pressure(15 mm.), last traces being removed by co-distillation with benzene (150 ml.). The acid chloride was dissolved in benzene (400 ml.), sodium azide (25 g., 0.304 mole) was slowly added, and the mixture was refluxed for 48 hours. After cooling, sodium hydroxide solution (3M, 100 ml.) was added and heating was continued for another 12 hours. The benzene was evaporated under reduced pressure (15 mm.) leaving a crude solid, which was collected, washed with cold water (50 ml.) and then dried *in vacuo* for 12 hours. The dry solid was thoroughly extracted with ether in a continuous Soxhlet extraction apparatus, and the crystals obtained by removal of the ether from the extract were crystallized from hot isopropanol, giving yellow prisms

(8.9 g., 36%), m.p. 112-115°. Recrystallization from hexane gave pure 1-aminofluorenone (8.6 g., 33%) as yellow needles, m.p. 118-120° (lit.,[46] m.p. 118.5^{o}). The i.r. spectrum showed ν max. 3290(>NH), 1680(>C=0), 1605, 1450, 1198, 750 cm^{-1}. The mass spectrum showed peaks at m/e = 197(1.9), 196(18), 195(100%)(M^{+}), 168(2.9), 167(6.6), 166(6.6), 140(9.6), 139(19.). ^{1}H n.m.r. ($CDCl_3$): 5.5δ (broad singlet; 2H) (exchangable with D_2O); 6.2 and 7.7δ (multiplet; 7H).

1-Chlorofluorenone

A mixture of hydrated copper sulphate (150 g., 0.92 mole) and sodium chloride (39 g., 0.68 mole) in water (480 ml.) was boiled 20 minutes until completely dissolved. An alkaline solution of sodium sulphite [from sodium bisulphite (31.8 g., 0.304 mole) and sodium hydroxide (21 g., 0.524 mole) in water (240 ml.)] was added to the resulting hot solution during about 20 minutes with constant shaking. The suspension was then cooled to room temperature in an ice-bath, and the supernatant liquid was decanted from the colourless cuprous chloride. The precipitate was washed twice by decantation with water containing a little dissolved sulphurous acid, the latter to prevent oxidation. The moist cuprous chloride was dissolved in concentrated hydrochloric acid (240 ml.) and stoppered to protect oxidation.

1-Aminofluorenone (8.8 g., 0.0446 mole) was dissolved in concentrated hydrochloric acid (20 ml.) and water (75 ml.) and the solution was cooled to 0° in an ice-salt bath with vigorous stirring and the addition of a little crushed ice. The salt, 1-aminofluorenone hydrochloride, separated as a finely-divided crystalline precipitate. During 10-15 minutes, a solution of sodium nitrite (10 g.) in water (20 ml.) was

added to the stirred suspension while the mixture was kept at 0-5° by the addition of a little crushed ice from time to time. The hydrochloride dissolved as the soluble diazonium salt was formed; the resulting solution was tested with potassium iodide-starch paper for the presence of free nitrous acid. The cold diazonium chloride solution was poured slowly and with shaking into cold cuprous chloride solution prepared above. The mixture was allowed to warm to room temperature without external heating, and was stirred occasionally. The mixture then was warmed 30 minutes on a water bath to about 80° with the occasional stirring to complete the decomposition of the double salt. Next day, the solid was filtered off, washed successively with 10% w/v sodium hydroxide solution (30 ml.), then water (3 x 30 ml.) and then dried <u>in vacuo</u> for 24 hours. The crude product showed 3 spots on t.l.c. ($CHCl_3$). Separation by column chromatography on Silica Gel (mesh 100-200) using ether-light petroleum (b.p. 60-90°) mixture (1:2) as eluant gave a pure yellow solid which crystallized from aqueous ethanol (50%) to give pure 1-chlorofluorenone (4.84 g., 50%) as yellow needles, m.p. 136-138° (lit.,[47] m.p. 137-138°). The i.r. spectrum showed ν max. 1701 (>C=0), 1604, 1197, 1097, 752(S), 741 cm^{-1}. The mass spectrum showed m/e = 217(2.3), 216(9.5) ($M^{+\cdot}$, ^{37}Cl), 215(6.0), 214(26) ($M^{+\cdot}$, ^{35}Cl), 189(3.0), 188(13), 187(9.5), 186(47) 152(15), 151(100%), 150(84.6), 149(10.7), 126(6.0), 125(18), 124(6.1), 123(13), 122(13), 121(6.5), 101(8.5), 100(10), 99(52), 98(59), 97(9.8), 87(53), 86(65), 85(23), 84(8.9), 76(23), 75(75), 74(97), 73(23), 63(47), 62(42), 61(29), 60(60), 51(53), 50(82), 39(70), 38(41), 37(25). ^{1}H n.m.r. ($CDCl_3$): 7.2δ -7.7δ (multiplet; 7H).

The crude yellow solid (1.0 g.) was also sublimed at 120°/15 mm. to give pure 1-chlorofluorenone (0.8 g.).

Reaction of 1-Chlorofluorenone with Potassium Amide in Liquid Ammonia

A solution of 1-chlorofluorenone (2 g., 0.094 mole) in dry tetrahydrofuran (60 ml.) was added to a stirred solution of potassium amide, prepared from potassium (3 g., 0.076 atom) in liquid ammonia (300 ml.), dried *in situ*. Stirring was continued for 4 hours and then ammonium chloride (5 g.) and ether (50 ml.) were slowly added to the violet solution. The ammonia was allowed to evaporate overnight at room temperature.

The residue was treated with water (150 ml.). Insoluble compounds (residue A) were filtered off, and aqueous solution (B) was extracted with ether (3 x 50 ml.) to give aqueous solution (C) and ethereal solution (D).

The residue (A) was extracted with ether (3 x 50 ml.) to give residue (E), and ethereal solution (F) which was combined with ethereal solution (D).

The solution (C) was acidified with 2N hydrochloric acid and then was evaporated *in vacuo* to give a white solid (6 g.), which was sublimed at 270°/0.3 mm. to give a white sublimate (0.41 g.). This was identified by i.r. spectrum and microanalysis as ammonium chloride. (Found: C, none; H, 7.54; Cl, 64.43. NH_4Cl requires H, 7.54; Cl, 66.06%). However, a trace of impurity, possibly 3-chlorobiphenyl-2-carboxylic

acid, was present in the sublimate, as shown by the mass spectrum: m/e = 234(37) (M^+, ^{37}Cl), 233(27), 232(90) (M^+, ^{35}Cl), 231(36), 217(35), 216(19), 215(81) (M^+ - OH), 198(32), 197(19), 181(32), 179(13), 153(32), 152(100%) (M^+ - COOH and - Cl), 151(41), 150(19), 105(50), 104(13), 77(47), 76(37), 75(26), 74(19).

The combined ethereal solutions (D) and (F), were then dried over anhydrous magnesium sulphate and evaporated to give a brown oil, which showed four spots on t.l.c. (Chloroform) [R_{f_1} = 0.60 (1-chlorofluorenone), R_{f_2} = 0.37(1-aminofluorenone), and two unknown materials R_{f_3} = 0.11 and R_{f_4} = 0.04]. Separation by column chromatography using benzene as eluant (Florisil, mesh 60-100) gave 1-chlorofluorenone (0.61 g., 31%); 1-aminofluorenone (0.47 g., 25%) and two unknown compounds (G) (0.32 g.).

The unknown compounds (G) (100 mg.) were mixed with acetic anhydride (0.5 ml.), glacial acetic acid (1 ml.) and zinc dust (1 mg.) and heated gently for 30 minutes on a steam bath, and then poured, whilst stirring, into cold water (20 ml.). After cooling in an ice-bath, the crude product was filtered off, washed well and dried. Crystallization from absolute ethanol gave a pale brown solid containing 3 compounds; t.l.c. ($CHCl_3$) showed that the two unknown compounds were still present, and the third one was 1-N-acetamido-9-fluorenone (see below).

The residue (E) was sublimed at 210°/0.3 mm. to give a sublimate (0.3 g.) containing starting material (1-chlorofluorenone), with some tar (0.21 g.) remaining.

N-1-acetamido-9-fluorenone

A mixture of 1-aminofluorenone (100 mg., 0.51 m mole), acetic anhydride (0.5 ml., 0.51 m mole), glacial acetic acid (1 ml., 1.0 m mole) and zinc dust (1 mg.) was heated gently for 30 minutes on a steam bath, and then poured, whilst stirring, into cold water (20 ml.). After cooling in an ice-bath, the crude product was filtered off, and washed well with a cold water (20 ml.) and dried. Crystallization of the yellow solid from absolute ethanol (20 ml.) gave a reference sample of N-1-acetamido-9-fluorenone (98 mg., 82%) as yellow needles, m.p. 134-136.5^{o} (lit.,[48] m.p. 136-137°). The i.r. spectrum showed ν max. 3320 (>N-H)(ω), 1705(>NHC-O), 1694(>C=O), 1610, 1520, 1411, 1305, 841, 782 cm^{-1}. The mass spectrum showed m/e = 239(1.9%), 238(16), 237(100%), (M^{+}), 223(1.3) (M^{+} - CH_2), 222(38) (M^{+} - CH_3), 221(2.1), 197(7.4), 196(90) (M^{+}- 41), 181(1.7), 180(2.3), 169(5.3), 168(37), 167(19), 166(21.), 165(5.5), 164(9.7), 152(5.2), 151(19), 150(10), 141(3.9), 149(26.), 139(76), 138(10.), 137(3.9), 127(4.8), 126(3.3).

(ii) 1-Chloroanthraquinone Section

Reaction of 1-chloroanthraquinone with Potassium Amide in Ammonia

A solution of 1-chloroanthraquinone (5 g., 0.02 mole) in dry tetrahydrofuran (200 ml.) was added to a stirred solution of potassium amide, which was prepared from potassium (5 g., 0.13 atom) in liquid ammonia (350 ml.), dried *in situ*. Stirring was continued for 4 hours and then ammonium chloride (5 g.) was added to the dark-red solution. The ammonia was allowed to evaporate overnight at room temperature.

The residue was treated with water (200 ml.). Insoluble compounds were filtered off, washed with chloroform (3 x 50 ml.) and the solid residue (A) was retained, after which the aqueous solution (B) was extracted with chloroform to give, with the chloroform washings above, chloroform solution (C) and aqueous solution (D). The combined chloroform solution (C) was extracted with 2N hydrochloric acid (3 x 50 ml.). The acid extracts were combined to give acid solution (E) and chloroform solution (F). The aqueous solution (D) was acidified and evaporated in vacuo to give inorganic salts (5.2 g.) (ammonium chloride and potassium chloride).

The acid solution (E)was basified with sodium hydroxide (20% w/v; 150 ml.) and extracted with chloroform (3 x 50 ml.) to give chloroform solution (G) and basic solution (H) which was discarded.

The chloroform solution (G) was made alkaline and dried over anhydrous magnesium sulphate, filtered and evaporated leaving a dark-red solid (3.7 g.). Separation was effected by column chromatography on alumina (neutral) using chloroform as eluant. The first eluted material was recovered starting material (0.56 g., 1.1%). The second eluted fractions were evaporated and the solid was crystallized from 95% ethanol to give pure 1-aminoanthraquinone (2.05 g., 45%) as red needles, m.p. 253-254° (lit.,[49] m.p. 253°). The i.r. spectrum showed ν max. 3398(>NH), 1675(>C=0), 1625, 1600, 1278, 700 cm^{-1}. The u.v. spectrum showed λ max. (EtOH) 234(logε = 4.30), 306(logε = 3.30), 497 mμ (logε = 3.43). The mass spectrum showed m/e = 225(1.6), 224(1.3) 223(100%) (M^{+}), 222(6.9), 195(13), (M^{+} - CO), 168(6.3), 167(15), 140(6.6), 139(12), 83(8.0), 77(3.0), 76(4.4), 75(3.5).

The third substance to be eluted was crystallized from 95% ethanol to give pure 2-aminoanthraquinone (1.21 g., 26%), as orange-red needles, m.p. 308-310° (lit.,[49] m.p. 308°). The i.r. spectrum showed ν max., 3325 (>NH), 1665(>C=0), 1630, 1600, 1276(S), 700 cm^{-1}. The u.v. spectrum showed λ max. (MeOH) 234(4.23), 298(3.92), 484 mμ (2.86). The mass spectrum showed m/e = 225(2.9), 224(17), 223(100%) (M^+), 222(9.4), 196(5.2), 195(25) (M^+ - CO), 194(9.4), 167(23), 166(11), 140(14), 139(34), 83(14), 77(4.7), 76(7.8), 75(5.6), 63(9.4).

The last eluates were collected and evaporated; t.l.c. ($CHCl_3$) showed the presence of two materials, which could not be recovered.

The residue (A) was sublimed at 190°/0.3 mm. to give a sublimate (0.8 g.) containing 1-aminoanthraquinone and 2-aminoanthraquinone, identified by using t.l.c. ($CHCl_3$) and i.r. spectra.

Evaporation of (F), which was made alkaline, gave a small residue which contained (t.l.c.) 1-aminoanthraquinone and 2-aminoanthraquinone.

Attempted Reaction of 2-chloroanthraquinone with Potassium Amide in Liquid Ammonia

2-Chloroanthraquinone (5 g., 0.02 mole) in dry tetrahydrofuran (200 ml.) was added to a stirred solution of potassium amide, which was prepared from potassium (5.2 g., 0.013 atom) in liquid ammonia (300 ml.) dried *in situ*. Stirring was continued for 4 hours and then ammonium chloride (5 g.) was slowly added to the green solution. The ammonia was allowed to evaporate overnight at room temperature.

The residue was treated with 2N hydrochloric acid (200 ml.) and extracted with chloroform (3 x 100 ml.) to give chloroform solution (A), residue (B) and acid solution (C).

The chloroform solution (A) was extracted with 20% v/v ammonium hydroxide solution (100 ml.) (ammonia, s g., 0.90) to give a basic solution (D) and chloroform solution (E), which was washed with water (3 x 100 ml.), dried and evaporated to give a solid (4.2 g.). Crystallization from benzene gave 2-chloroanthraquinone (4.1 g., 82%)(starting material).

The residue (B) was extracted with chloroform (4 x 50 ml.) to give residue (F) and chloroform solution (G), which was combined with chloroform (E) above. The residue (F) was tarry (0.10 g., m.p. over 360°) and no material could be sublimed from it.

The acid solution (C) was evaporated <u>in vacuo</u> to give inorganic salts.

The basic solution (D) was extracted with chloroform (3 x 50 ml.) to give solution (H) and chloroform solution (I), which was washed with water (3 x 50 ml.), dried over magnesium sulphate, filtered and evaporated to give a yellow solid (50 mg.); t.l.c. ($CHCl_3$) showed the presence of starting material and an unknown material which was not identified.

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A P P E N D I X

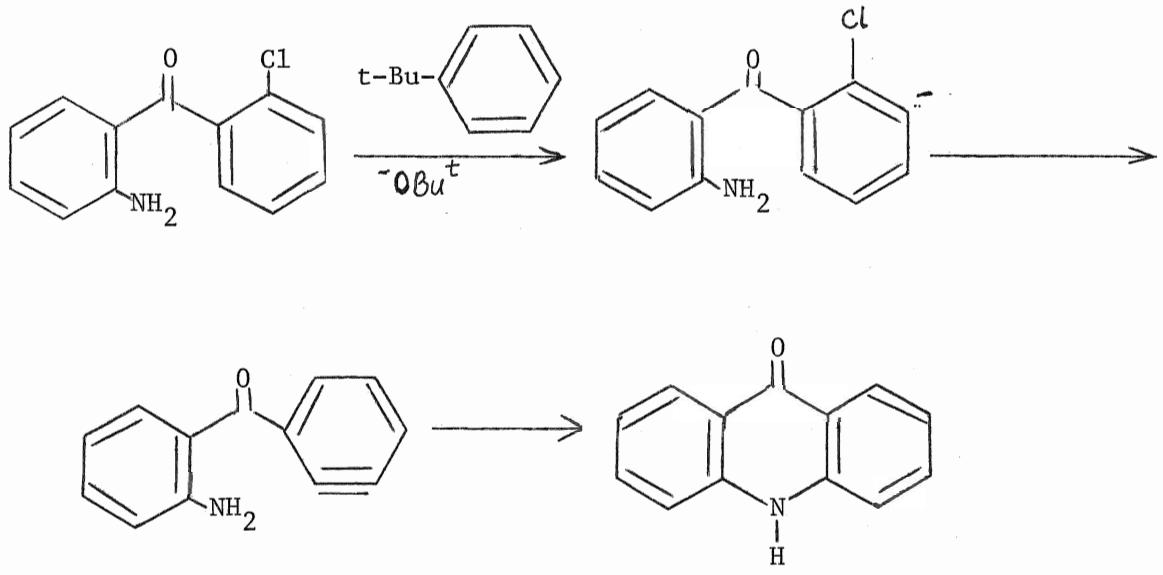
APPENDIX

Attempts to cyclise 2-amino-2'-chloro- and 2-amino-3'-chlorobenzophenone with potassium amide in liquid ammonia in dry ether failed, as recorded on pages 60 and 61 respectively. Cadogan and coworkers[50] have noted the formation of arynes from various aryl halides and potassium t-butoxide in t-butylbenzene as solvent. After the main thesis work was finished, these conditions were applied to 2-amino-2'-chloro- and 2-amino-3'-chlorobenzophenone respectively.

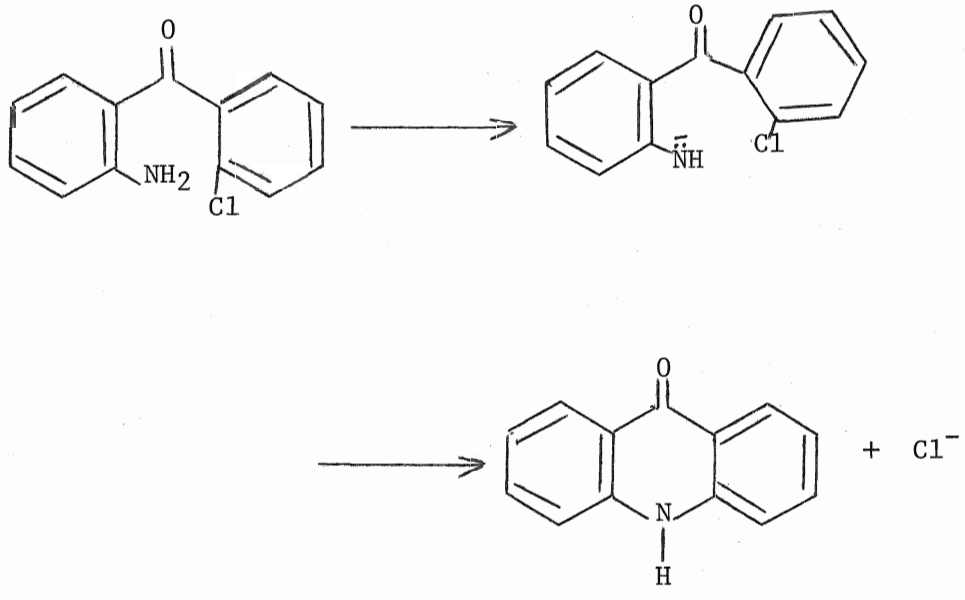
Reaction of 2-Amino-2'-chlorobenzophenone with Potassium t-Butoxide

2-Amino-2'-chlorobenzophenone and potassium t-butoxide in t-butylbenzene as solvent were boiled under reflux overnight under nitrogen. The resulting suspension was evaporated and the crude solid was washed with water and dried *in vacuo*. Crystallization from ethanol gave a dark green solid, (78%), m.p. 345-352°. The crude solid was sublimed at 230°/0.5 mm. to give yellow plates, m.p. 347-355°. This compound was identified as acridone by comparison with a sample prepared by Drozdov's method[51]. The i.r., mass, and u.v. spectra of both samples were identical (Acridone).

Via Benzyne intermediate

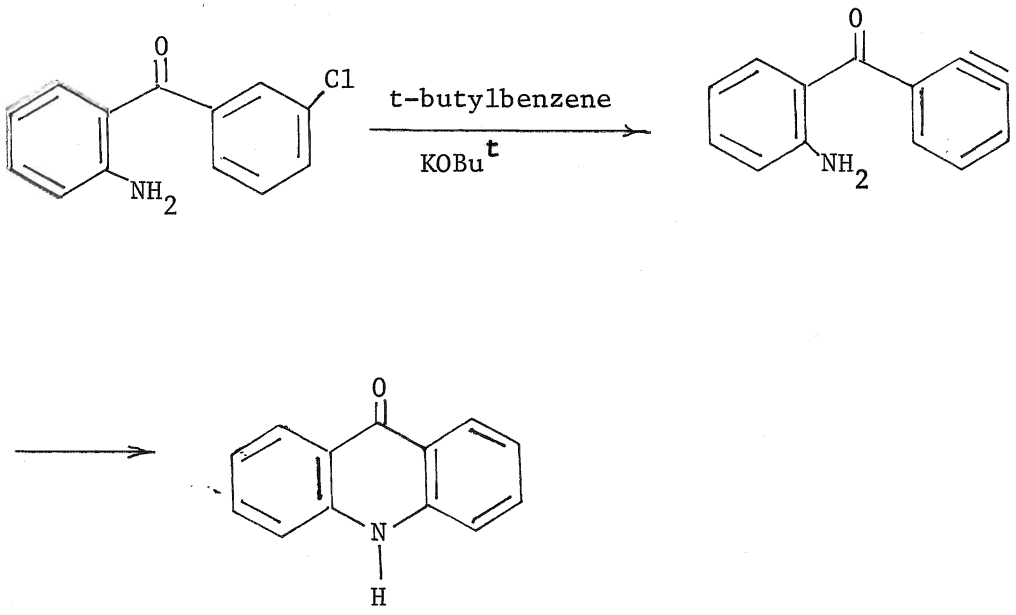


Via nucleophilic substitution



Reaction of 2-Amino-3'-chlorobenzophenone with Potassium t-Butoxide

2-Amino-3'-chlorobenzophenone was treated with potassium t-butoxide and t-butylbenzene, and boiled under reflux overnight, under nitrogen. The resulting suspension was evaporated to leave a crude solid which was washed with cold water and dried *in vacuo*. Crystallization from ethanol gave a dark green solid, which t.l.c. showed to contain two compounds ($CHCl_3$). Separation by column chromatography on Florisil (benzene as eluant) gave pure acridone; the second was not identified. Sublimation of the acridone at 210°/0.5 mm. gave yellow plates (35%), m.p. 354-357, (lit.,[51] m.p. over 360°).



EXPERIMENTAL

Preparation of Potassium t-butoxide

Potassium (1.3 g., 0.033 mole) was slowly added, to a 500 ml. three-necked-flask, equipped with condenser and drying tube, thermometer, and inlet for nitrogen gas, containing t-butanol (2.4 g., 0.033 mole). The mixture was stirred for 2 hours and the solvent was then evaporated under reduced pressure (15 mm.). The crude product (1.3 g., quantitive yield) was kept dry for the next step.

Reaction of 2-Amino-2'-chlorobenzophenone with Potassium t-butoxide

2-Amino-2'-chlorobenzophenone (1.6 g., 0.0051 mole), potassium t-butoxide (1.10 g., 0.011 mole), and t-butylbenzene (50 ml.) were boiled under reflux with stirring under nitrogen. After 12 hours, a suspension had formed. The solvent was distilled from the mixture under reduced pressure (15 mm.). The crude adduct was collected, washed with water (30 ml.), and dried *in vacuo*. Crystallization from 95% ethanol gave a dark green solid (1.1 g., 78%), m.p. 335-350°. The crude green solid was sublimed to give pure acridone as yellow plates, m.p. 340-355°. The i.r. spectrum showed ν max. 3098(ω), 1605(>C=0), 1595, 1549, 1523, 1452, 731 cm^{-1}. The mass spectrum showed m/e = 196(22.), 195(100%), (M^{+}), 194(4.1) (M^{+} - 1), 168(29), 167(12) (M^{+} - CO), 140(9.8), 139(12), 83.5(9.8), 83(1.5) 82.5(2.4), 77(5.4), 76(4.1), 75(4.1), 74(2.9). The u.v. spectrum showed λ max. (MeOH), 379(log ε = 3.94) and 396 mμ (log ε = 3.94).

Reaction of o-Chlorobenzoic Acid with Aniline to Synthesize Acridone

o-Chlorobenzoic acid (4 g., 0.025 mole), dry potassium carbonate (4 g.), aniline (13 g., 0.140 mole), and copper powder (0.01 g.) were heated together at 120° for 3 hrs., and then the reaction mixture was poured into 10% v/v hydrochloric acid (30 ml.) to give crude diphenylamine-2-carboxylic acid. A mixture of the crude acid (6.8 g.), phosphoryl chloride (1.5 g., 0.009 mole), and xylene (20 ml.) was refluxed (oil bath) until the liberation of hydrogen chloride had stopped. The xylene was then evaporated and the residue was digested with cold aqueous potassium carbonate solution. Filtration gave acridone (4.5 g., 72%), m.p. 355-360°, as the insoluble product. Sublimation of the crude compound gave acridone as yellow needles, m.p. 360-365°. The i.r. spectrum showed ν max. 3087(>NH), 1615(>C=0), 1590, 1549, 1523, 1450, 739 cm^{-1}. The mass spectrum showed m/e = 196(22), 195(100%) (M^+), 174(4.1) (M^+ - 1), 168(29), 167(12) (M^+ - CO), 169(9.8), 139(12), 83.5(9.8), 83(1.5), 82.5(2.4), 71(5.4), 76(4.1), 75(4.1), 74(2.9).

Reaction of 2-Amino-3'-chlorobenzophenone with Potassium t-butoxide

2-Amino-3'-chlorobenzophenone (1.4 g., 0.0049 mole) was dissolved in t-butylbenzene (30 ml.); potassium t-butoxide (0.82 g., 0.0074 mole) was slowly added and the mixture was then boiled under reflux with stirring under nitrogen. After 12 hours, a suspension had formed. The solvent was distilled from the mixture under reduced pressure (15 mm.). The crude adduct was collected, washed

with water (30 ml.), and dried *in vacuo*. Crystallization from 95% ethanol gave a dark green solid (0.56 g., 79%), m.p. 290-339°; t.l.c. ($CHCl_3$) showed the presence of two materials, one of which was acridone. Separation by column chromatography on Florisil using benzene as eluant gave from the second fraction, almost pure acridone (0.41 g., 35%) as yellow plates. Sublimation of this fraction gave pure acridone as yellow needles, m.p. 354-357° (lit.,[51] m.p. over 365°). The i.r. spectrum showed ν max. 3089(ω), 1615(>C=0), 1595, 1545, 1520, 1455, 731 cm^{-1}. The mass spectrum showed m/e = 196(14), 195(73) (M^+), 194(32), 167(28)(M^+ - CO), 166(82) (M^+ - HCO), 165(64), 164(86), 140(38), 139(55), 138(45), 137(16), 83(34), 82.5(82), 82(10), 77(31), 76(23), 75(39), 74(27), 44(100%). The u.v. spectrum showed λ max. (MeOH), 379(log ε = 3.90), 396 mμ (log ε = 3.84). The other reaction product was not completely freed from acridone and was not identified.

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