SYNTHESIS OF 3-BROMO-6-NITROFLUORENONE

by

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To My Beloved Parents

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ABSTRACT

A synthesis of 3-bromo-6-nitrofluorenone has been accomplished and the evidence that 2-nitrofluoranthene brominated in the 9-position has been confirmed. The theoretical implications of these results have been discussed. As a result of this work nine new compounds have been prepared, namely, 4-nitro tosyl anthranilic acid, 4-bromo-2-methyl-4'-nitrobenzophenone, 5-bromo-2-(p-nitrobenzoyl) benzoic acid, 5-bromo-2-(p-nitrobenzoyl) benzoyl chloride, 5-bromo-2-(p-nitrobenzoyl) benzamide, 2-amino-4-bromo-4'-nitrobenzophenone, 3-bromo-6-nitrofluorenone, 3-bromo-6-nitrofluorenone oxime, 4-bromo-2-hydroxy-4'-nitrobenzophenone.

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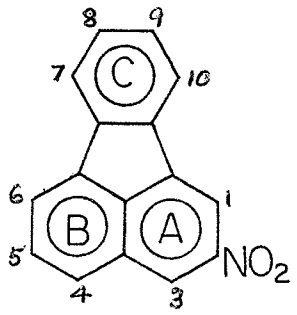
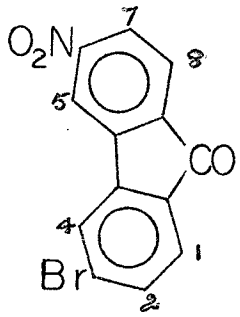
INTRODUCTION

In 1965, in these laboratories A. Dolenko (20) studied the bromination of 2-nitrofluoranthene (I). The bromo-2-nitro-derivative thus obtained, on oxidative degradation, gave a compound which on theoretical grounds appeared to be 3-bromo-6-nitrofluorenone (III).



(I)



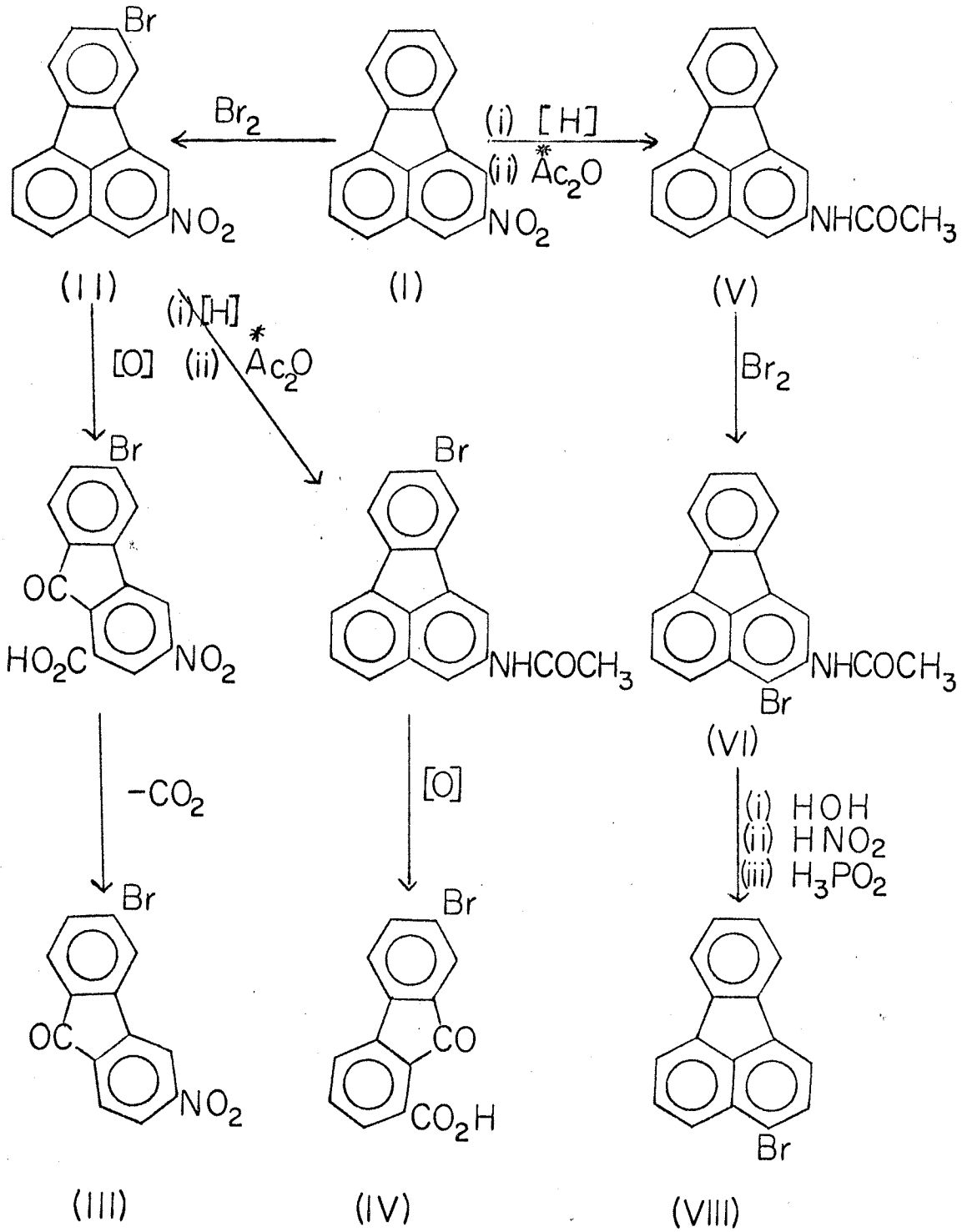
(III)

If so, this would establish that the bromination of fluoranthene had occurred in the C-ring and in the 9-position. As 3-bromo-6-nitrofluorenone has not been reported in the literature, it seemed very desirable that its synthesis should be undertaken by a method or methods that would leave no doubt as to its orientation. A comparison could then be done with Dolenko's product. The synthesis of this substance forms the content of this thesis.

In the past few years the preparation and the orientation of disubstituted fluoranthenes has been the subject of careful study in this laboratory and in many other laboratories. This work has revealed some directive properties of the fluoranthene nucleus. The studies on

3-substituted fluoranthenes by Campbell and Keir (13) led to the generalization that a meta-directing group in ring A of fluoranthene would direct a second substituent to the 9-position. Furthermore an ortho-para-directing group in the same ring would direct a second substituent to the 8-position. The work of Kloetzel, King and Menkes (47) necessitated a modification of the above generalization, that a strongly activating group in ring A, should cause further substitution in the same ring. This was later substantiated by the work of Charlesworth and Blackburn (14) who found that 3-amino and 3-acetamidofluoranthenes brominated in the 2-position.

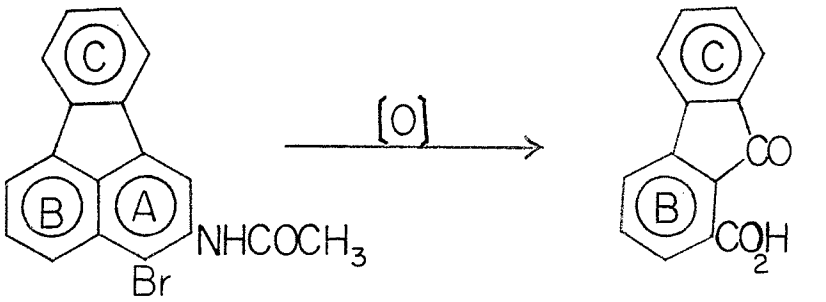
Dolenko (20) extended the study to determine the directive properties of 2-substituted fluoranthenes. The results on the directive effects of nitro (a deactivating and meta-directing) and acetamido (a strongly activating) groups in the 2-position were shown to be in accordance with the above mentioned rules; i.e., 2-nitrofluoranthene brominated in the 9-position as expected from Campbell's generalization, and 2-acetamidofluoranthene was brominated in the 3-position according to Kloetzel's modification. The orientations of bromine in the brominated fluoranthenes were established according to the scheme on page 3. The bromo-fluorenone-carboxylic acid (IV) was shown to be identical with an authentic sample of 7-bromo-fluorenone-1-carboxylic acid, thus showing that bromine was in the 9-position of the fluoranthene. The oxidation of the 9-bromo-



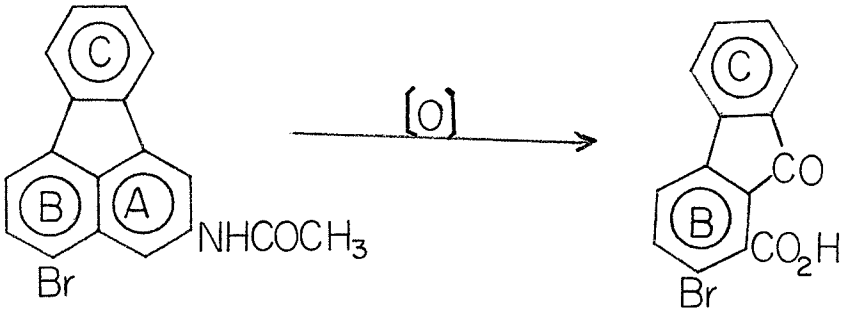
* Ac_2O — $(CH_3CO)_2O$

2-nitrofluoranthene (II), followed by the decarboxylation of the oxidation product to the bromo-nitrofluorenone (III) was also carried out with the hope of obtaining an additional evidence. The bromine in the 9-position of the fluoranthene would give 3-bromo-6-nitrofluorenone. The present work has shown the identity of the bromo-nitrofluorenone (III) to 3-bromo-6-nitrofluorenone, thus confirming the evidence that 2-nitrofluoranthene brominated in the 9-position.

The orientation of bromine in the 2-acetamido-bromo-fluoranthene (VI) was established (20) by converting it to the bromofluoranthene (VIII). This bromofluoranthene was shown to be identical with 3-bromofluoranthene, thus indicating that bromine was either in the 3-position or in the 4-position. So far there have been no instances in which a substituent has been shown to enter the B-ring (i.e., 4, 5 and 6-positions). Therefore it was concluded by Dolenko (20) that the bromine was in the 3-position. This conclusion could be confirmed by carrying out an oxidation in the acetamido-bromo-fluoranthene stage. 2-Acetamido-3-bromo-fluoranthene (VI) would give the fluorenone-1-carboxylic acid (VII), because the ring A being electronically rich, would be more susceptible to oxidation than the rings B and C. Whereas 2-acetamido-4-bromofluoranthene (VIa) would give 2-bromo-fluorenone-1-carboxylic acid (VIIa), because again the ring A, being activated by the acetamido group, would be degraded during oxidation.



(VI) (VII)



(VIa) (VIIa)

Time did not permit either Dolenko or the writer to perform this oxidation, but it would seem very desirable that it should be tried by some other worker in the near future.

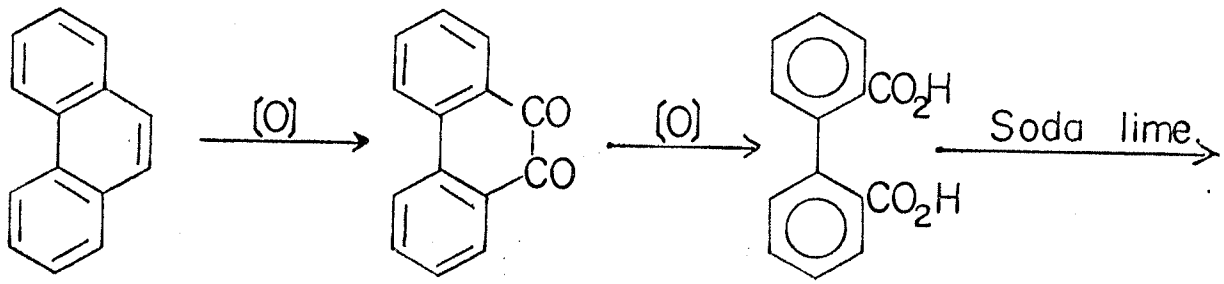
LITERATURE SURVEY

(1) The Discovery and the Structure of Fluorene

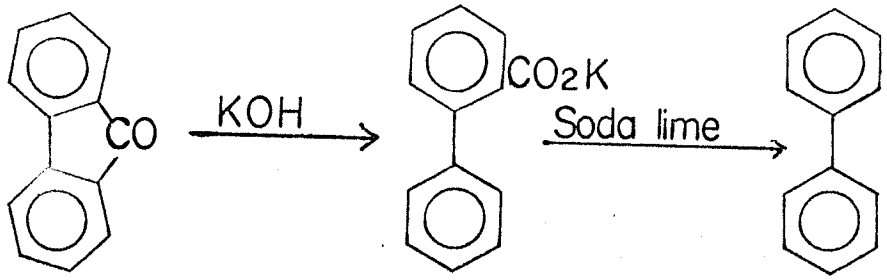
The chemistry of fluorene began at a comparatively early date in the history of organic chemistry. During his memorable researches on the pyrogenetic hydrocarbons, in 1867 Berthelot (9) isolated a new substance from the fraction of crude anthracene oil boiling between 300 and 310°C. This substance on recrystallization from hot ethanol gave a white fluorescent solid melting at 113°C. Because of the fluorescence Berthelot named it as "Fluorene". However, in 1883 Hodgkinson and Mathews (41) showed that the fluorescence was due to the presence of some impurity which was removed by recrystallization from glacial acetic acid or by sublimation over potassium carbonate.

The discovery of phenanthrene (IX) in 1872 by Fittig and Ostermayer (31) and independently in the same year by Graebe (35), played an important role in the prompt elucidation of the constitution of fluorene. Fittig and Ostermayer (32) carried out the following degradation, leading to the known biphenyl (XII). (See next page for the flow sheet). The compound resulting from the action of soda lime on the then unknown diphenic acid (X) was rightly interpreted as biphenylene ketone (XI) [m.p. 83.5 - 84°C].

Fittig (27) distilled the biphenylene ketone with zinc dust and found that it was reduced to a white substance melting at 113-114°C. He regarded this compound as

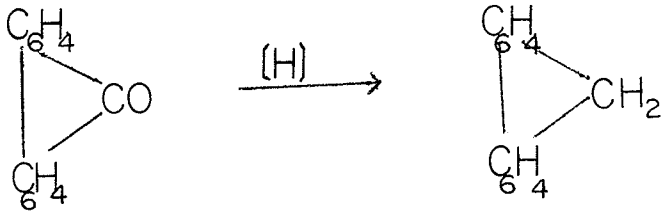


(IX) (X)



(XI) (XII)

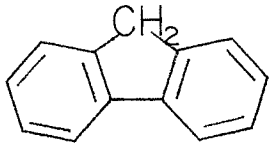
biphenylene methane (XIII).



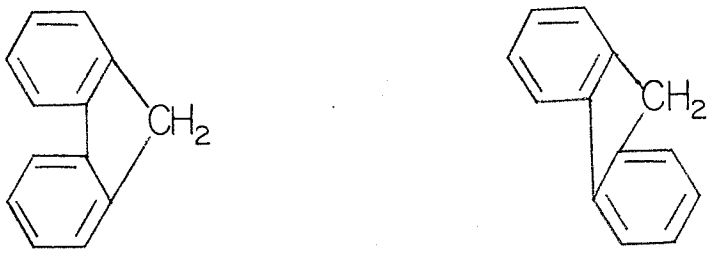
(XI) (XIII)

Graebe (36), using the biphenylene ketone of Fittig, carried out the reduction with red phosphorus and hydriodic acid and obtained the same hydrocarbon. Barbier (5) observed that the compound obtained by the oxidation of fluorene with potassium dichromate and sulphuric acid was identical with the biphenylene ketone of Fittig and Ostermayer.

In 1878, Fittig and Schmitz (33) reported that the biphenylene methane previously obtained by Fittig from the biphenylene ketone was identical with fluorene obtained by Berthelot and Barbier. Hence the structural formula of fluorene could be represented as:



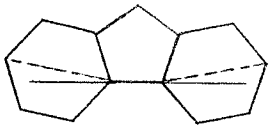
In 1925, Kuhn and Jacob (49) proposed a space formula for fluorene (XIV) based on Kaufler's formula for diphenyl in order to explain their claimed separation of two forms of 9-amino fluorene.



(XIV)

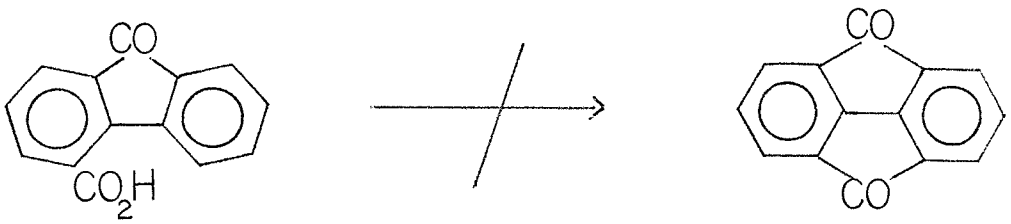
Since then, there has been extensive investigation of the possibility of stereoisomerism of 9-substituted fluorenes. All such attempts have failed or been disproved, so that such extreme forms as pictured in (XIV) seems unlikely if not impossible.

Mills, Palmer and Tomkinson (56) suggested that a strainless configuration for the fluorene molecule could be achieved by the planes of the benzene rings becoming inclined to the 5-membered ring. The stereochemical implications of such a non-planar structure have been widely investigated, with some equivocal results, reviewed by Cook and Iball (17). But the evidence does seem to indicate that the rings are bent away from the coaxial diphenyl bond with a distortion of the valence angles from the benzene rings by 12°, to give (XV) a planar structure as pictured by Pinck and Hilbert (64), where the five membered ring is nearly a regular pentagon.

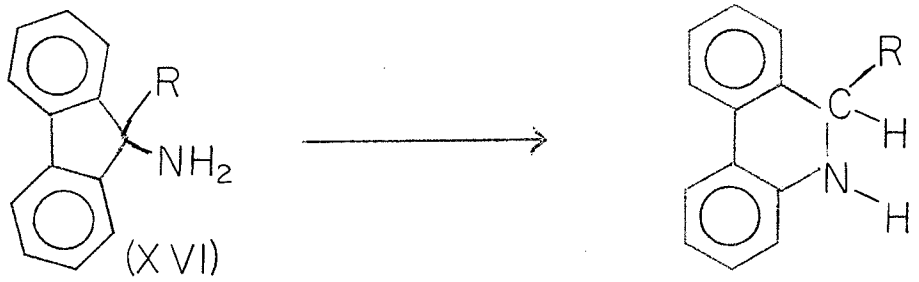


(XV)

This formula is probable from dipole measurements (8), (42) and x-ray studies (39) and is further supported by the failure of fluorenone-4-carboxylic acid to close a fourth ring (56), the distance being too great to be bridged.

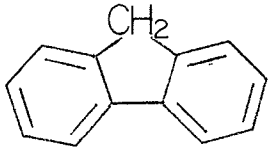


Such a planar configuration as (XV) would be in a state of strain and has been used (64) to account for the ready enlargement of the five-membered ring in the Stieglitz rearrangement of the amines of the type (XVI) to yield phenanthridines.



(XVI)

Mills and Nixon (55) suggested that this internal strain could be relieved at least partially by a preferred arrangement of the double bonds as shown in (XVII).



(XVII)

Evidence favouring this formula is scant but may be found in the ring closures of γ-2-fluorylbutyric acid (48) and of o-(2-fluoryl)-benzoic acid (7) both of which take place into the 3-position. These facts seemed to indicate that the double bond in fluorene is located entirely between positions 2 and 3 as shown in (XVII).

From the above discussion, it is evident that the problem of the bond structure of fluorene is similar to that of naphthalene, anthracene, etc., and like them fluorene should be susceptible to attack by the methods used by Fieser and Lothrop (22), (23), (24), (25) which depend on the Claisen rearrangement of allyl ethers and the diazo coupling

of the hydroxyl derivatives.

A preliminary investigation (51) of the rearrangement of the allyl ethers of 2-hydroxyfluorene and 3-hydroxyfluorene indicates that the aromatic ring in fluorene is benzenoid rather than naphthoid and it is suggested that the special reactivity of positions 2- and 7- may be ascribed to the superior directive properties of the phenyl group.

(2) Oxidation of Fluorene

Fluorenone, the main oxidation product of fluorene has been obtained in a number of ways.

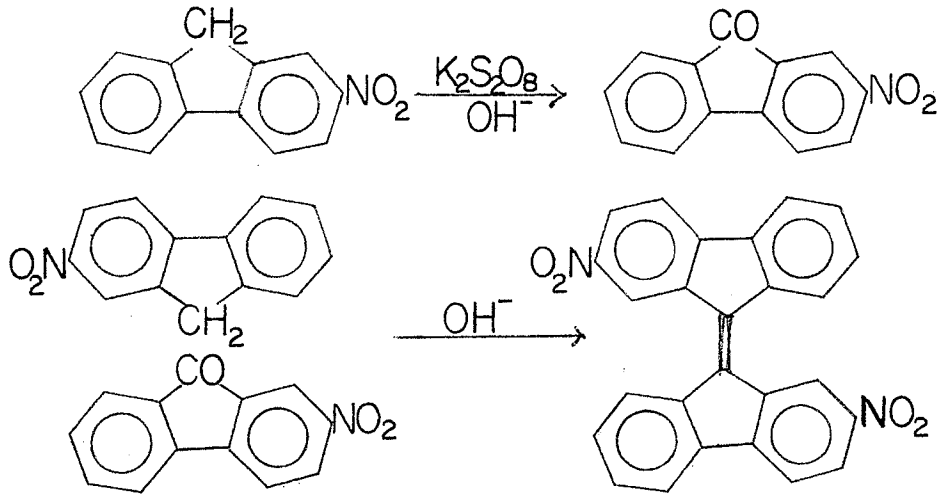
(a) Huntress, Herschberg and Cliff (46) used sodium dichromate in acetic acid as the oxidising agent and obtained fluorenone in good yields. This method is suitable for large scale laboratory preparation of fluorenone.

(b) Postowski and Lugowkin (65) have shown that fluorene on oxidation with selenium oxide gave only 5% fluorenone.

(c) Courtot (18) used solutions of potassium permanganate at room temperature to oxidise fluorene and derivatives to the corresponding fluorenones. The yields were mostly quantitative.

(3) Gutmann, Butle and Fenton (37) studied the oxidation of fluorene, 2-acetamido fluorene and 2-nitro-fluorene by alkaline potassium persulphate solutions. They found that fluorene and 2-acetamido fluorene

were resistant to oxidation whereas 2-nitrofluorene was attacked at the methylene carbon to yield 2-nitrofluorenone and 2,2'-dinitro-9,9'-bifluorylidine.



Since of the three fluorene derivatives investigated only 2-nitrofluorene which has a strongly electron attracting substituent on the nucleus was attacked, it appears that successful oxidation of fluorene compounds by persulphate depends upon the formation of an anion.

(e) Wheeler (73) used chromyl chloride as an oxidising agent and obtained fluorenone in 35% yield.

(f) Sprinzak (71) observed that when a solution of fluorene in pyridine was stirred in an atmosphere of oxygen at room temperature in the presence of a small amount of Triton B, one mole of oxygen per mole of fluorene was absorbed with heat evolution and fluorenone was formed in almost quantitative yield. The reaction was not sensitive to light and started without an induction period.

This high reactivity may be attributed to the presence of appreciable concentration of carbanions recognizable by the colour of their solutions.

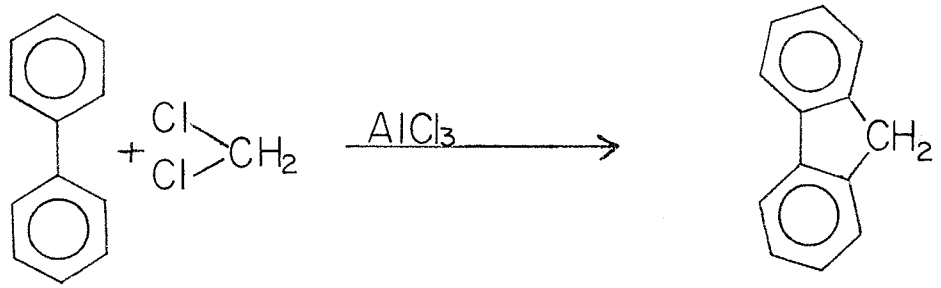
(g) Recently Ogata, Kotake and Aoki (60) in their investigation of peracetic oxidations of polynuclear aromatic compounds, found that fluorene on oxidation with peracetic acid gave a dihydroxy fluorenone. The positions of the two hydroxyl groups are still uncertain.

(3) Synthesis of Fluorenones

(a) Oxidation of Fluorenes

Fluorenones may be obtained by the oxidation of fluorenes by methods described in the previous section. So the methods of formation of fluorenes could be extended as a synthetic route to fluorenones, by including the oxidation step. Hence the formation of fluorenes is considered first.

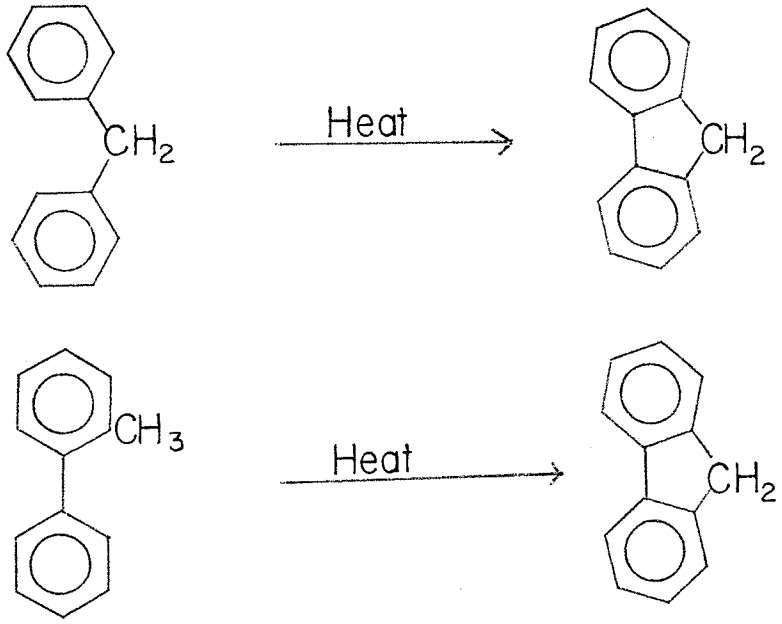
In 1886, Adam (2) showed that biphenyl and methylene dichloride in a Friedel-Crafts reaction yielded fluorene. The reaction indicated very well the structure of fluorene and its close relationship to biphenyl.



The synthesis of new biphenyl derivatives has led to the

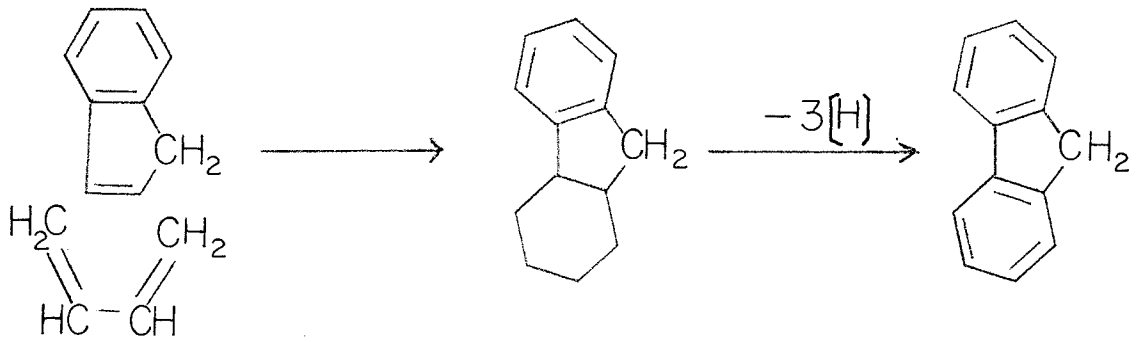
successful preparation of fluorenone and fluorene derivatives with substituents in 3, 4 and 6 positions (63).

Fluorenes are also obtained by the cyclodehydrogenation, usually by heating to a high temperature in the presence of a catalyst, of diphenyl methane and of o-methyl biphenyls (61), (62), (63).



Longo and Pirona (50) have made a study of the synthesis of fluorene compounds from biphenyl derivatives and in particular the influence of the positions of substituting groups on the formation of fluorene structures. They were able to prepare 1-methyl fluorene and 1, 6-dimethyl fluorene through the synthesis of some then new biphenyls.

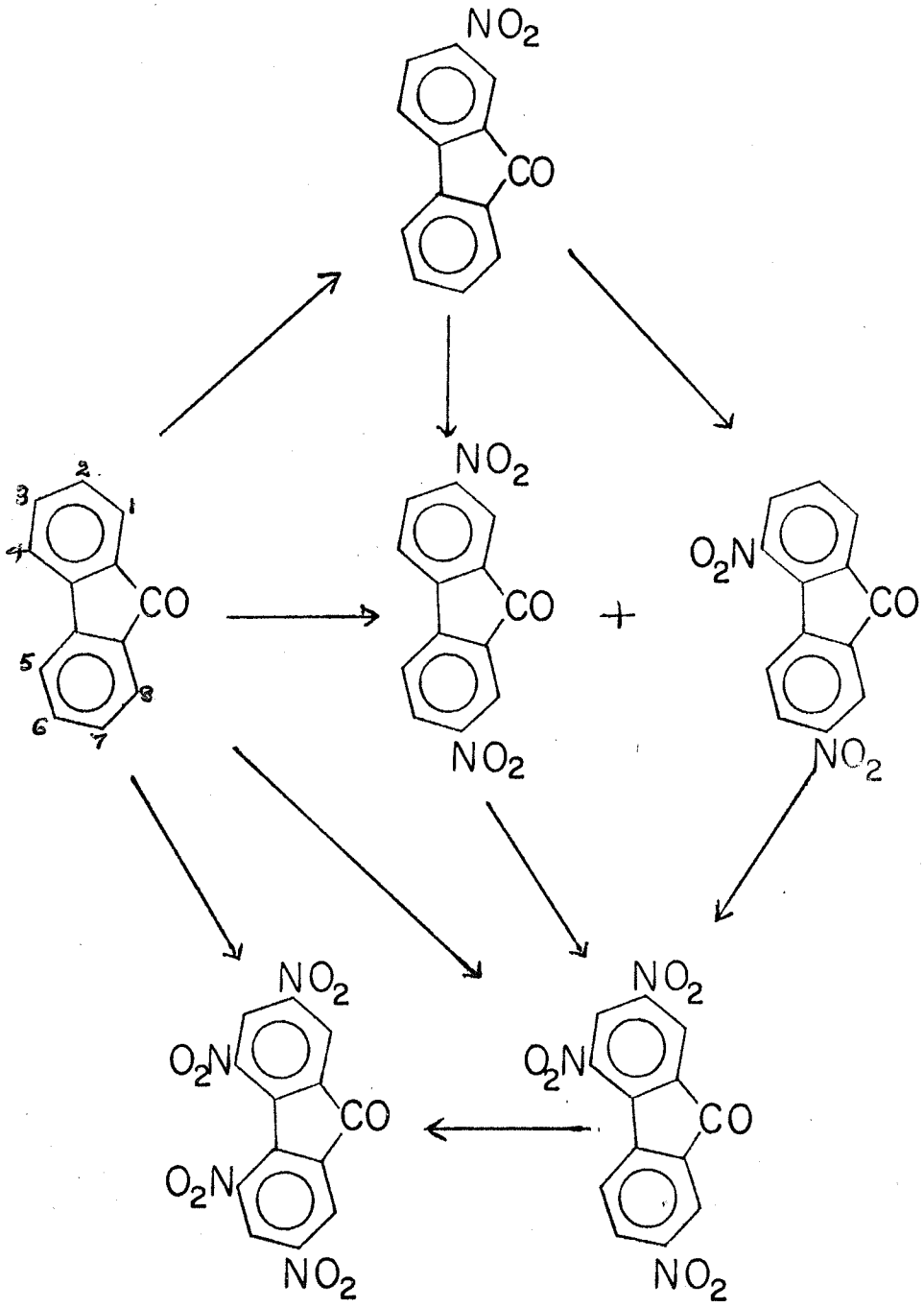
Another synthesis of fluorenes involves a "diene" addition of butadiene to indene to give a tetrahydrofluorene (3) which on dehydrogenation gives fluorene.



A synthesis of limited scope involves the application of Mannich reaction to α-indane derivatives. Harradence and Lions (38) prepared a few fluorene derivatives by the above method.

(b) Direct Substitution

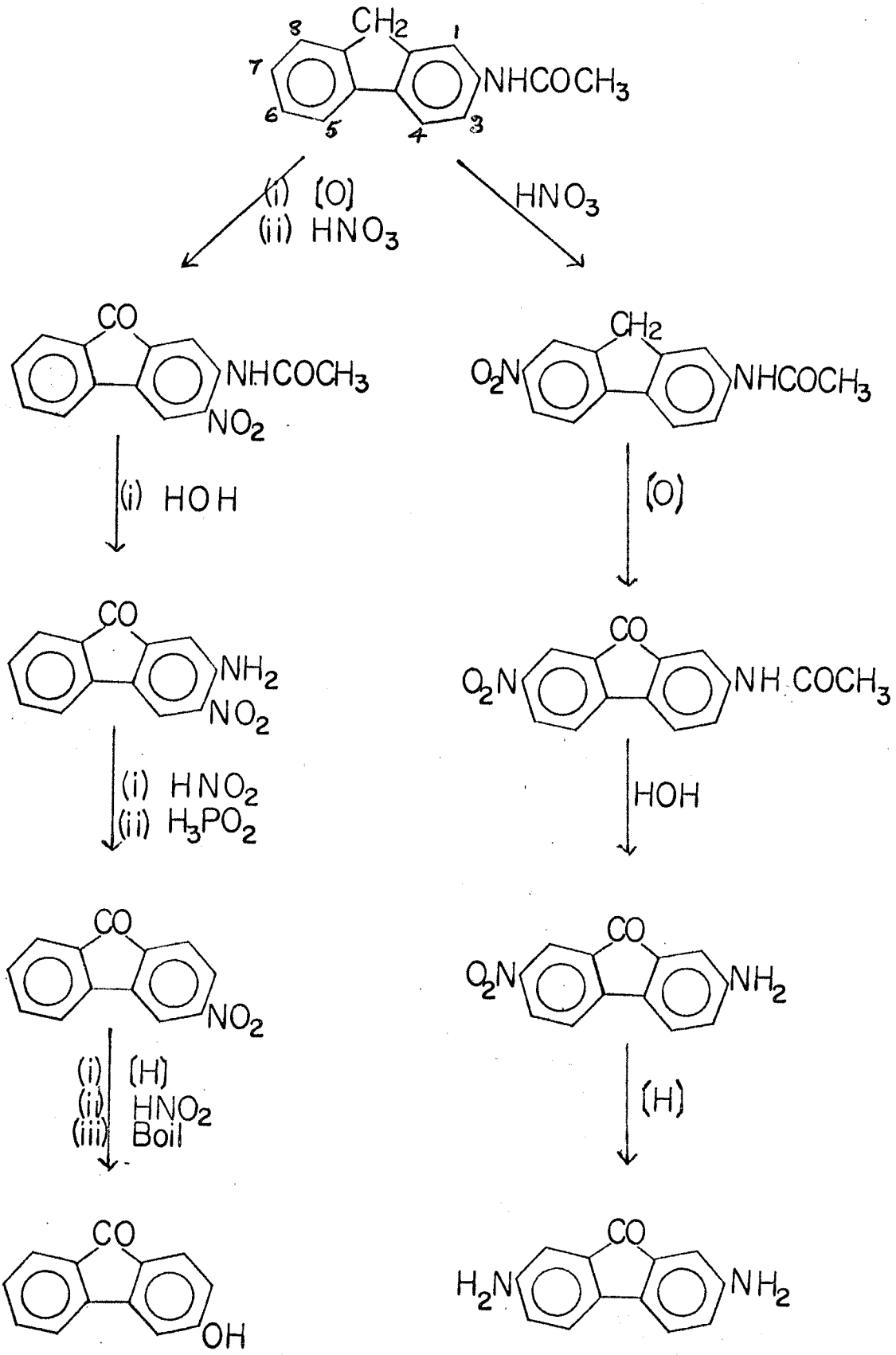
Fluorenones may also be prepared by direct substitution on fluorenone or on fluorene followed by oxidation. Originally this method was used to prepare 2- and 2, 7- substituted fluorenones. But substitution studies on both fluorene and fluorenone indicated that this method may also be used to prepare 3- and 3, 6- substituted fluorenones. It is also worthwhile to note that this method suffers from the marked disadvantage in the separation of the mixture of fluorenones formed. For example, consider the nitration of fluorenone. The various nitration products formed, are as shown in the scheme on the following page. The aforementioned scheme may be used to obtain fluorenones with substituents in 2, 4, 5 and 7 positions. The 3-, and 3, 6- substituted fluorenones have been obtained by a slight variation in the method of


NO2
CO
2
3
1
4
CO
5
8
6
7
NO2
CO
NO2
+
O2N
CO
NO2
NO2
O2N
CO
O2N
NO2
NO2
O2N
CO
NO2

nitration.

Diels, Schill and Tolson (19) investigated the action of nitric acid on 2-acetamido fluorene. A mixture of two mono nitro products was obtained. Saponification yielded two amino-nitro fluorenones which were widely different in basicity. The more basic one was found to be 2-amino-7-nitro fluorenone. The less basic compound was reported as 2-amino-1-nitro fluorenone. Twenty-six years later Eckert and Langecker (21) showed that this compound was really 2-amino-3-nitro fluorenone by converting it to the previously known 3-hydroxyfluorenone. Their work is summarized in the flow sheet on the following page. Eckert and Langecker (21) also investigated the nitration of other derivatives of fluorene involving the 2-position. 2-Acetamido fluorenone gave results analogous to 2-acetamido fluorene. 2-Amino-fluorenone, however, gave only 2-amino-7-nitro fluorenone.

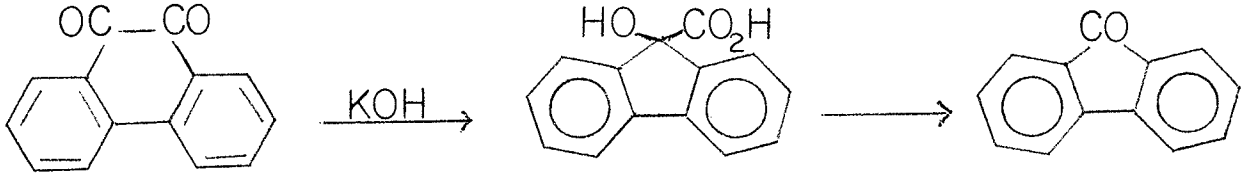
Barker and Barker (6) prepared some 3, 6-disubstituted fluorenones by following a procedure, similar to that used by Eckert and Langecker, starting from 2, 7-diacetamidofluorene and 2, 7-diacetamido fluorenone. Both these compounds behaved in a similar manner in many respects. The dinitration of 2, 7-diacetamido fluorenone gave only one compound, namely 2, 7-diacetamido-3, 6-dinitro fluorenone. This compound was converted to the dinitrofluorenone by hydrolysing the acetamido groups and deaminating the diamine formed. The orientation of the nitro groups was confirmed by converting the above dinitro fluorenone to the dibromo fluorenone,


CH2
NHCOCH3
(i) [O]
(ii) HNO3
HNO3
CO
NHCOCH3
NO2
(i) HOH
CH2
O2N
NHCOCH3
(O)
CO
NH2
NO2
(i) HNO2
(ii) H3PO2
CO
O2N
NH COCH3
HOH
CO
NO2
(i) [H]
(ii) HNO2
(iii) Boil
CO
O2N
NH2
(H)
CO
OH
CO
H2N
NH2

which was shown to be identical with 3, 6-dibromo fluorenone obtained from 3, 6-dibromo phenanthraquinone. This work is summarized in the flow sheet on the following page.

(c) From Phenanthraquinones

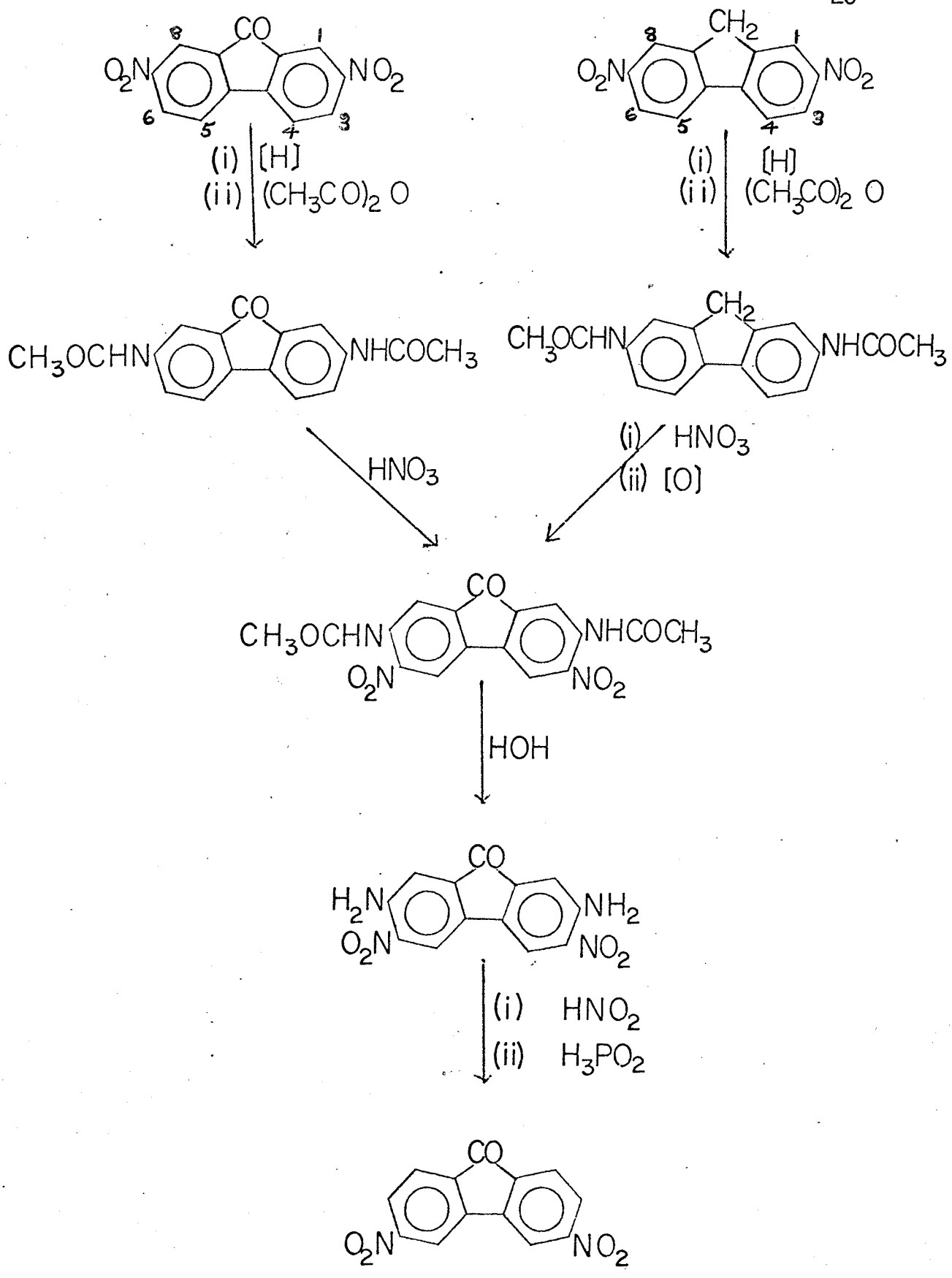
The conversion of phenanthraquinone into derivatives of fluorenone has proved to be one of the most reliable methods. Phenanthraquinone bearing structural similarity to open chain α-diketones undergoes bezilic acid rearrangement giving biphenylene glycollic acid. The latter compound, an α-hydroxy acid, oxidises readily to fluorenone.



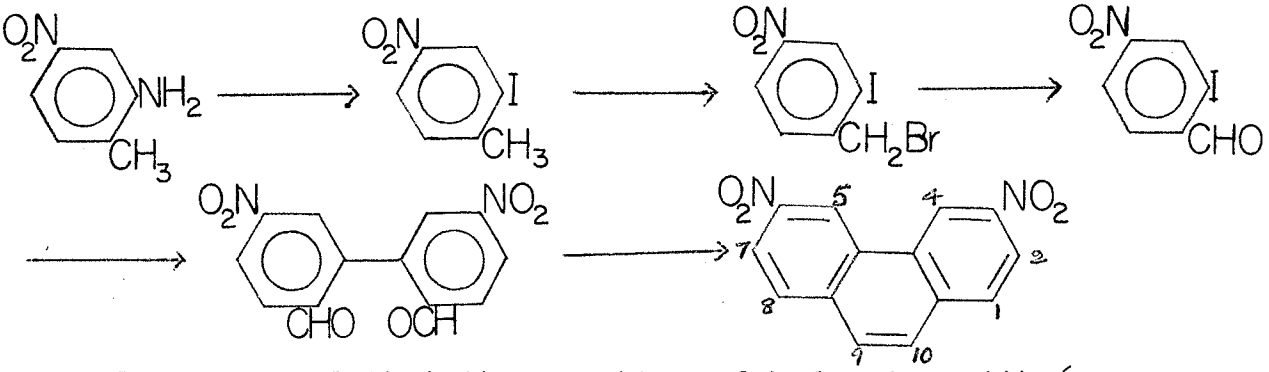
This oxidation could be brought about by boiling with water or alkalis in the presence of air. The passage from phenanthraquinone directly to fluorenone was accomplished with alkaline permanganate (10).

Schmidt and Bauer (69), (70) using appropriate derivatives of phenanthraquinone, carried out a number of syntheses. They observed that the nature of the substituents in the phenanthraquinone molecule had a definite effect upon the ease with which the rearrangement took place.

This method was limited by the fact that many of the desired phananthraquinones were not known. In the past ten years, the rapid development of phenanthrene chemistry has led to newer methods for the synthesis of substituted

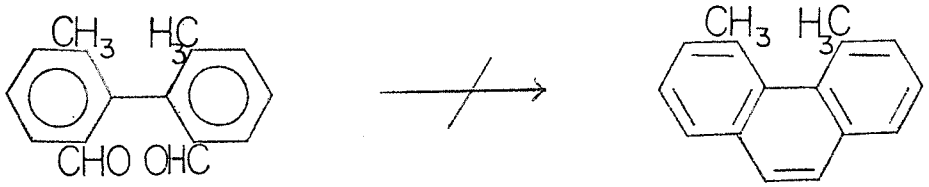

CO
O_2N
NO_2
(i) [H]
(ii) $(CH_3CO)_2O$
CH_2
CH_3OCHN
$NHCOCH_3$
HNO_3
(i) HNO_3
(ii) [O]
HOH
H_2N
NH_2
(i) HNO_2
(ii) H_3PO_2

phenanthrenes. In 1958, Bacon and Lindsay (4) discovered a new route to phenanthrenes from substituted diphenyl- 2, 2'-dialdehydes, by reductive cyclisation using hydrazine. They studied in some detail the conversion of diphenyl -2, 2'-dialdehyde into phenanthrene in polar solvents (e.g. ethanol and acetic acid), in the presence of mineral acid or of alkali, and in their absence, at temperatures ranging from below zero to above 100°C. Approximately one mole of nitrogen was evolved per mole of phenanthrene produced. In boiling acetic acid the conversion of dialdehyde into phenanthrene was quantitative. When the yield was not quantitative the by-products were soluble resins and a yellow polyazine. The study indicated that the formation of polyazines was favoured by low temperatures, absence of acid or alkali, and use of dioxan as the reaction medium. They extended the applicability of this reductive cyclisation to the synthesis of 3, 6-dinitrophenanthrene in the following manner starting from 2-amino-4-nitro toluene.



They also observed that the reaction of hydrazine with 6, 6'-dimethyl-diphenyl-2, 2'-dialdehyde failed to give 4, 5-dimethyl phenanthrene. This may be attributed to steric

factors, associated with the methyl groups in the two other ortho positions.

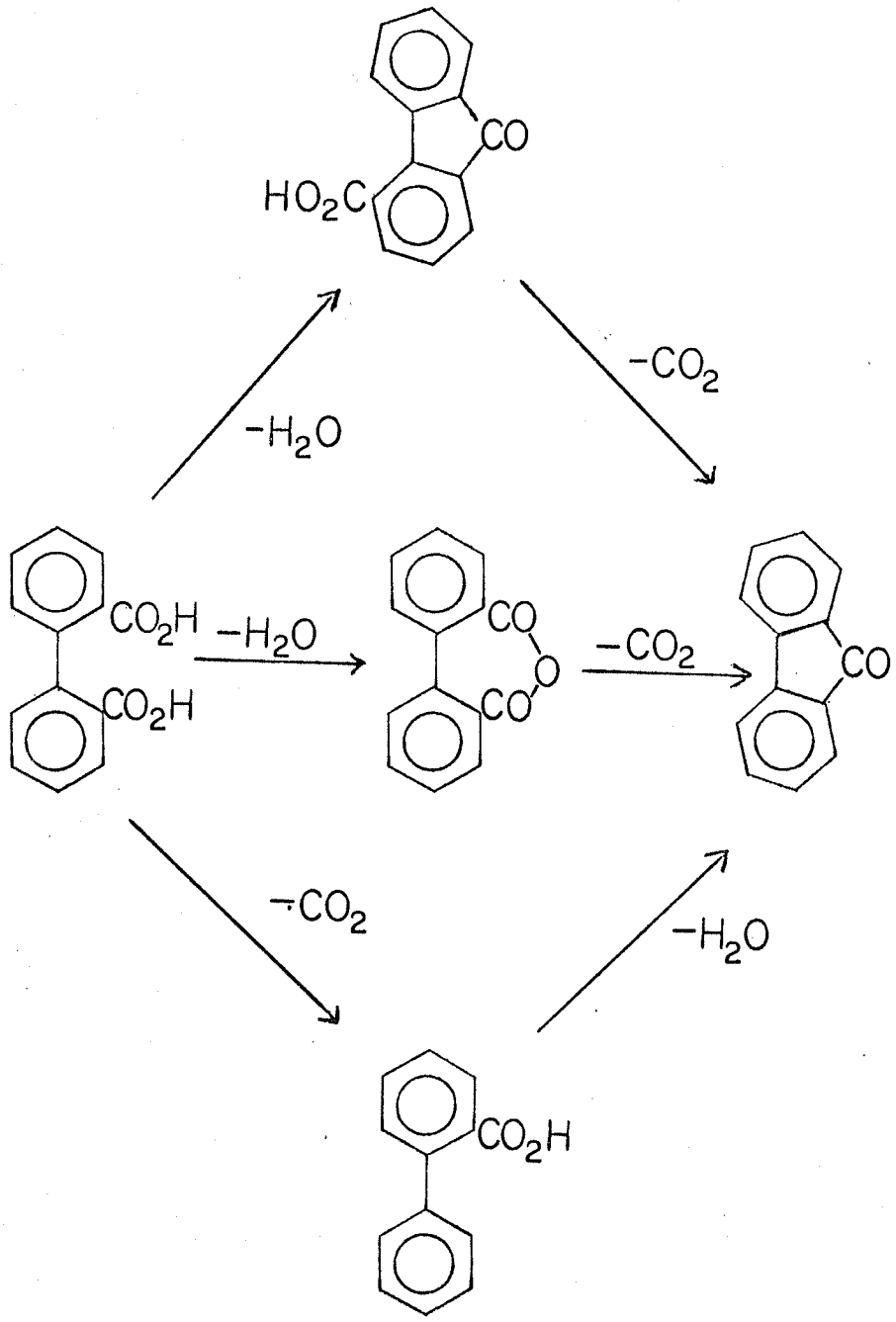


The substituted phenanthrenes may be oxidised to the corresponding phenanthraquinones which in turn could be converted to fluorenones.

(d) From Diphenic Acids

Fluorenone of high purity has been obtained by Huntress, Herschberg and Cliff (46) by heating diphenic acid at 360°C. At the above temperature the transformation has been rapid and quantitative. The transformation may take place in three ways as shown on the following page. No conclusion as to the mechanism of the reaction could be drawn, because under the same conditions both fluorenone-4-carboxylic acid and diphenic acid gave the same result.

Huntress and Cliff (44) succeeded in preparing a number of dichloro-fluorenones from various dichloro diphenic acids and their anhydrides. For example 3, 6-dichloro fluorenone was obtained by the pyrolysis 5, 5'-dichloro diphenic anhydride. 1, 8-dichloro fluorenone was obtained in quantitative yields from the action of heat on 3, 3'-dichloro diphenic anhydride, however, when 3, 3'-dichloro diphenic acid was heated the product was 1, 6-dichloro-fluorenone-5-carboxylic acid, from which 1, 6-dichloro


HO2C
CO
-CO2
-H2O
CO2H
CO2H
-H2O
CO
O
CO
-CO2
CO
-CO2
-H2O
CO2H

fluorenone could be obtained by further heating. The sequence of reactions are as shown on the flow sheet to follow.

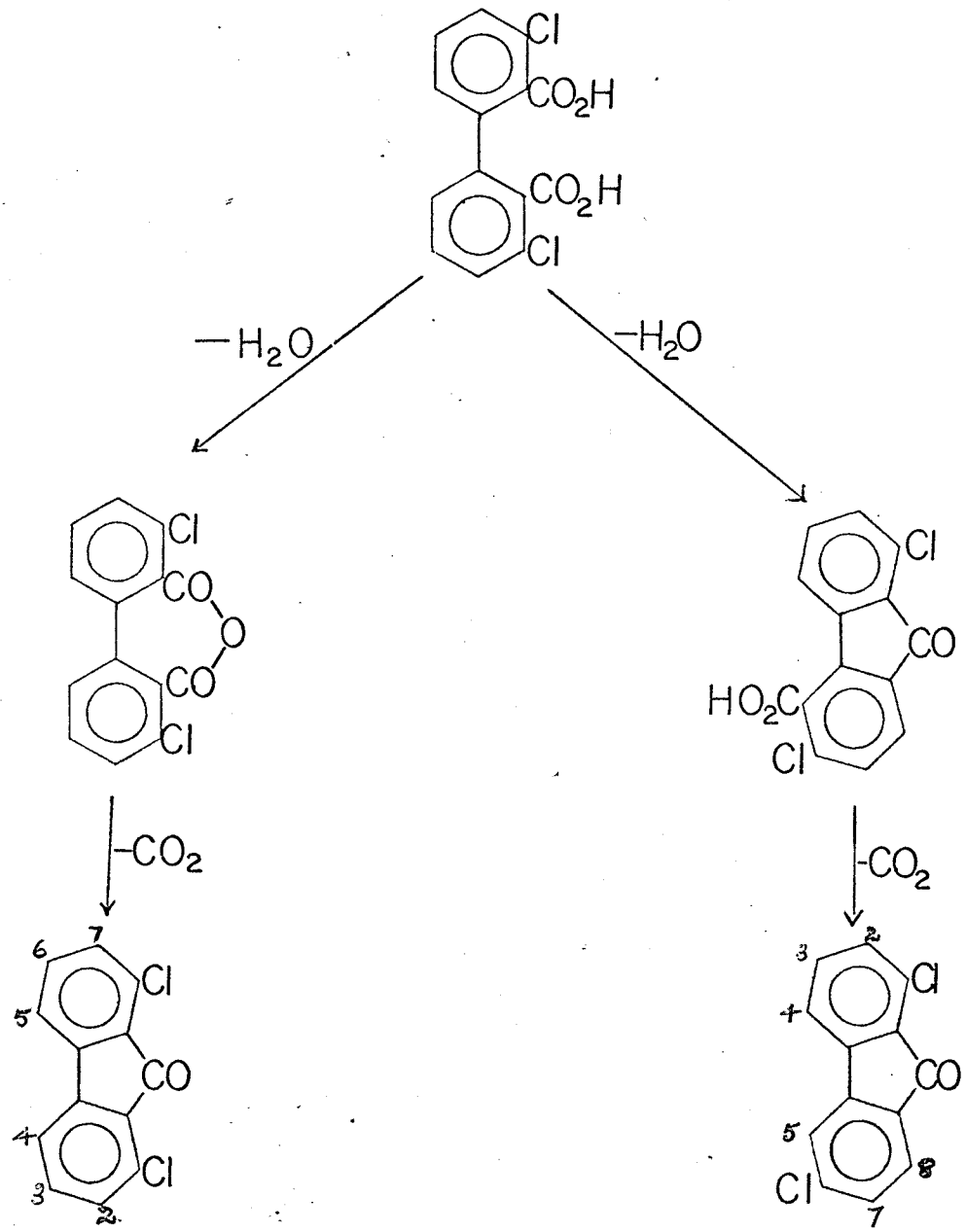
Huntress, Cliff and Atkinson (45) extended the study of 3, 3'-dichloro diphenic acid and investigated the action of concentrated sulphuric acid upon it. At 125°C the expected 1, 6-dichloro fluorenone-5-carboxylic acid was obtained, but when the temperature was raised to 170°C a dichloro fluorenone-carboxylic acid, "Acid X" was obtained which was different from 1, 6-dichloro-fluorenone-5-carboxylic acid. In other words, "two isomeric mono basic acids were obtained at different temperatures by the same procedure from the same starting material." Two other interesting facts were also noted:

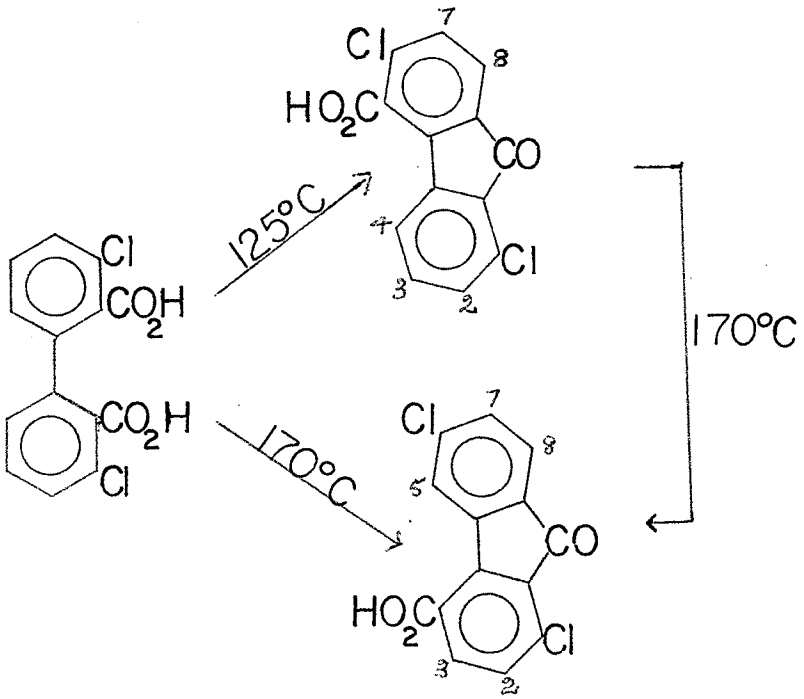
(1) On redissolving 1, 6-dichloro-fluorenone-5-carboxylic acid in concentrated sulphuric acid and heating at 170°C, "Acid X" was formed in a 67 percent yield.

(2) When "Acid X" was decarboxylated, the product was found to be 1, 6-dichlorofluorenone.

These facts show that during the isomerisation to "Acid X" both the fluorenone nucleus and the relative position of the two halogen atoms in it are preserved.

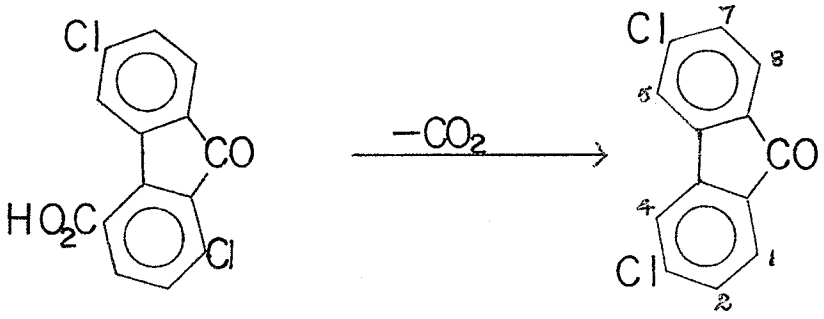
Later Huntress and Atkinson (43) established the constitution of "Acid X" as that of 1, 6-dichloro fluorenone-4-carboxylic acid. These results emphasize the danger in the use of high temperatures in the synthesis of fluorenones.


Cl
CO2H
CO2H
Cl
−H2O
−H2O
Cl
CO
O
CO
Cl
HO2C
Cl
CO
Cl
-CO2
-CO2
6
7
5
Cl
CO
4
Cl
3
2
3
2
4
Cl
CO
5
8
Cl
7

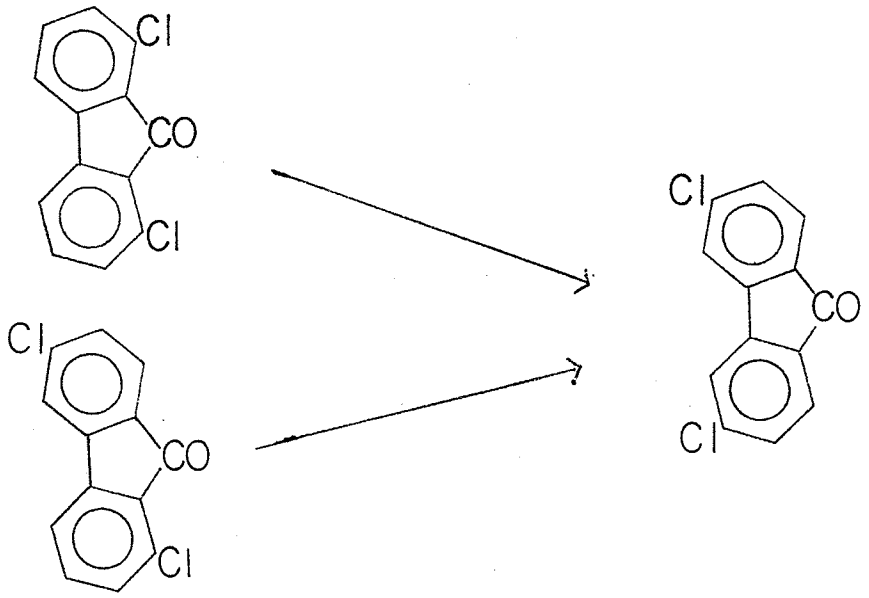


Acid X

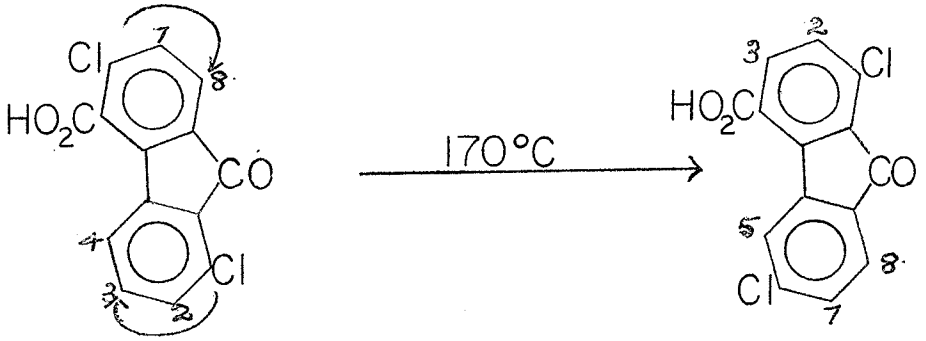
The decarboxylation of 1, 6-dichloro-fluorenone-4-carboxylic acid in sulphuric acid gave 3, 6-dichloro fluorenone.



Further experiments showed that both 1, 8-dichloro fluorenone and 1, 6-dichloro fluorenone rearranged to 3, 6-dichloro fluorenone on heating in sulphuric acid at 185-200°C.

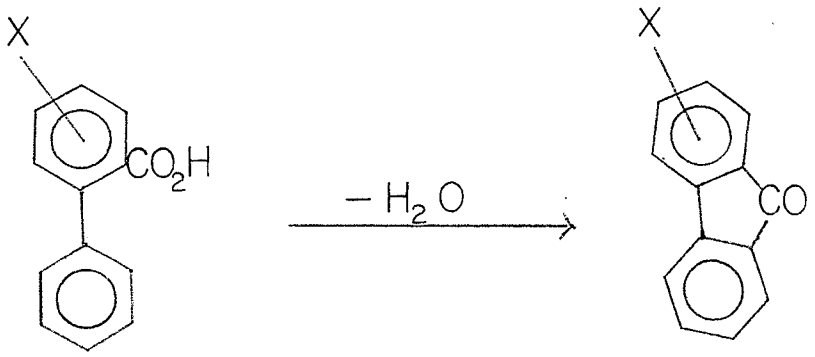


These rearrangements are unusual, for rearrangements involving meta transpositions are rare. From these series of experiments one would expect the isomerisation of 1, 6-dichloro fluorenone-5-carboxylic acid to 1, 6-dichloro fluorenone-4-carboxylic acid involves the migration of halogens.

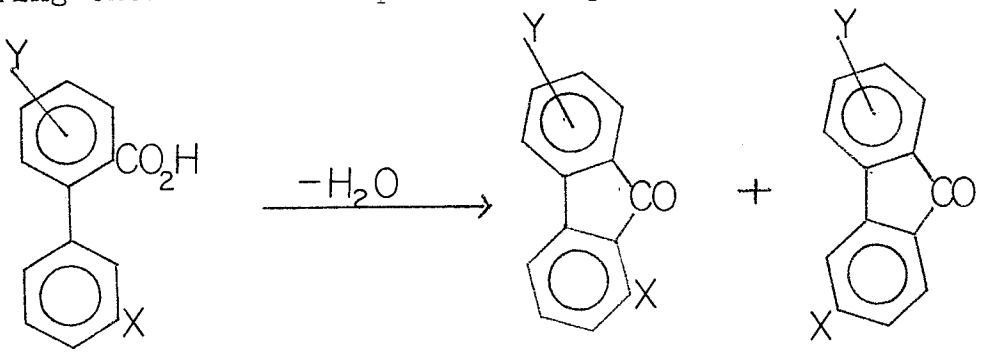


(e) From O-Carboxy Biphenyl Derivatives

The dehydration of O-carboxy biphenyl derivatives constitutes another method which is of particular value because of the high yields. The ring closure is usually effected with concentrated sulphuric acid.

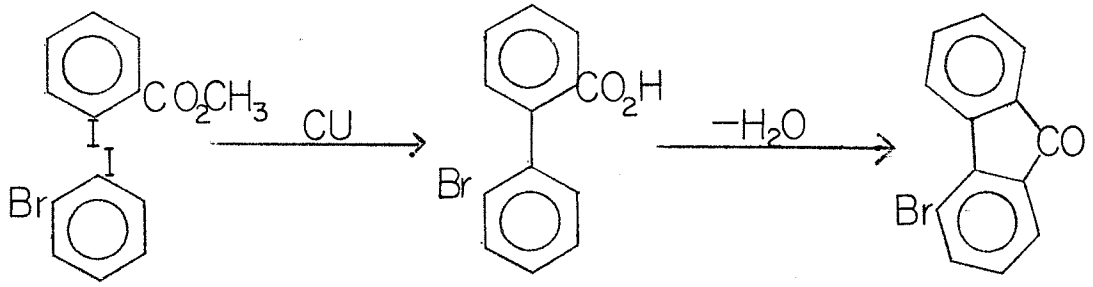


A distinct disadvantage is encountered in this method if the substituent in the second ring is in the meta position, as on ring closure two compounds are possible.

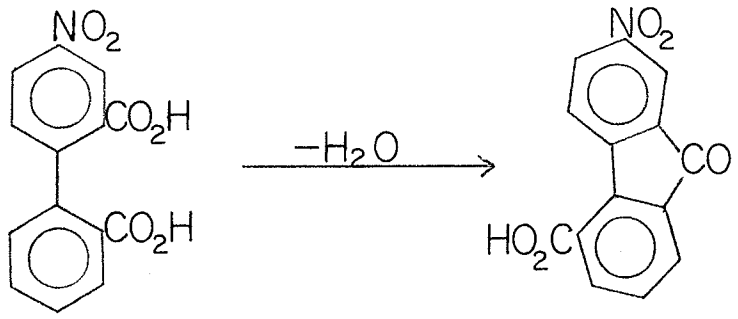


No complications are involved, however, if the substituents are in the first ring or in the ortho and para positions of the second ring.

Miller and Bachmann (54) obtained 4-bromo fluorenone from 2-bromo,-2'-carboxy-biphenyl in quantitative yields using concentrated sulphuric acid.

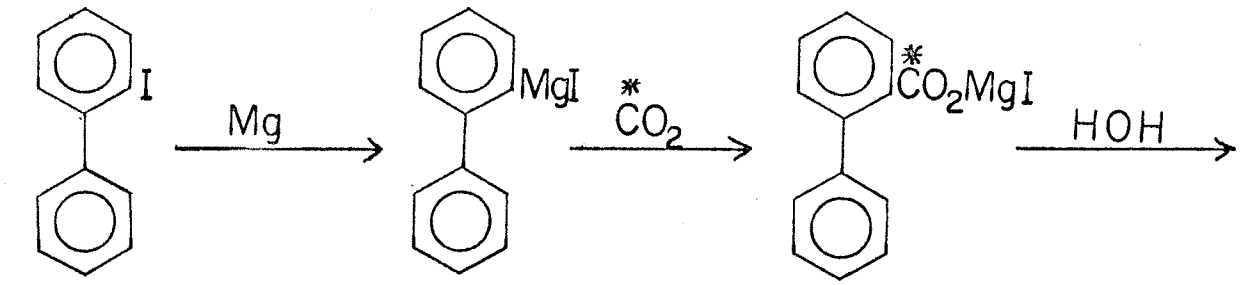


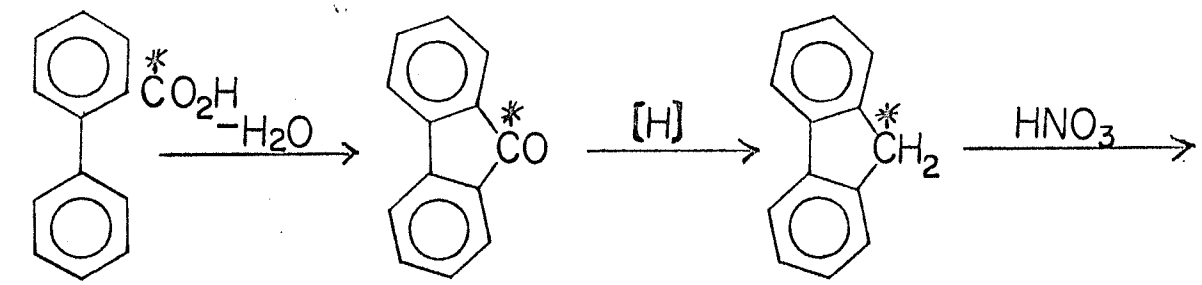
When substituted diphenic acids were used, a substituted fluorenone-carboxylic acid was obtained. Moore and Huntress (59) prepared 7-nitro fluorenone-4-carboxylic acid from 4-nitro diphenic acid.

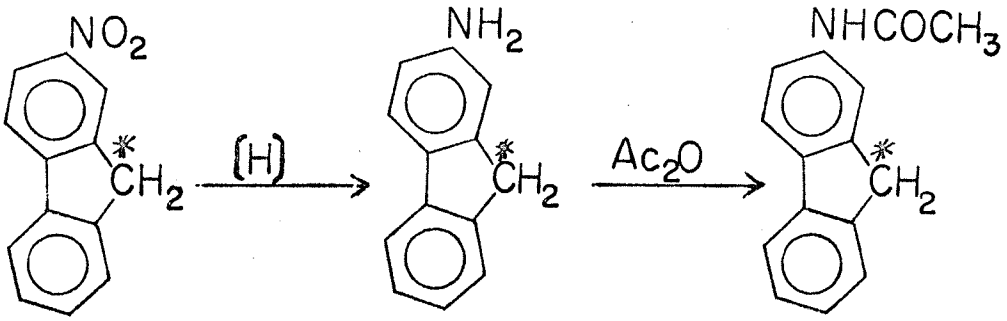


Sampey and Reid (67) used this method along with direct nuclear substitution in the synthesis of 2-acetyl amino fluorene from 2-Iodo biphenyl with radioactive carbon 14 in the 9-position of the molecule. The sequence of reactions are as shown on the following page. The labelled 2-amino-fluorene and 2-acetamidofluorene are widely used in Cancer research.

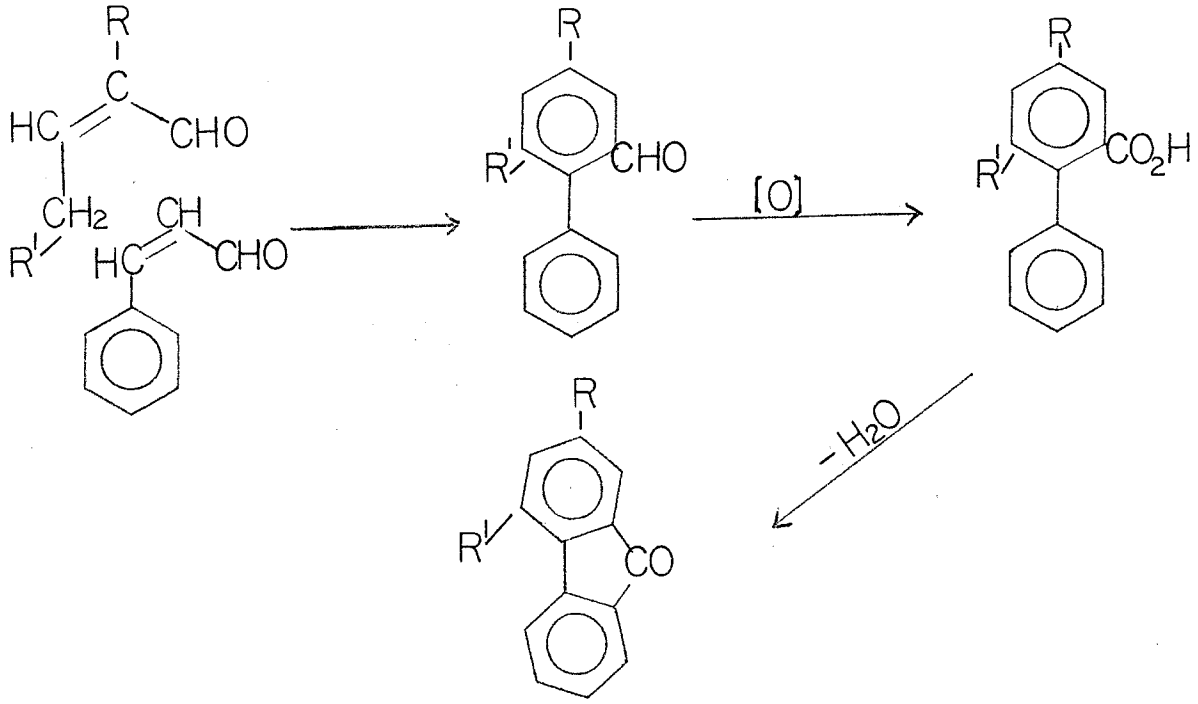
Recently Wiemann and Godfroid (74), (75) showed that when compounds of the general formula $R^1CH_2CH = C.R.CHO$ were condensed with cinnamaldehyde at 400°C in the presence of magnesium oxide, 2, 4-substituted biphenyl aldehyde (with traces of cyclohexadiene which was detected by Vapour phase


I
Mg
MgI
*CO2
*CO2MgI
HOH


*CO2H
-H2O
*CO
[H]
*CH2
HNO3

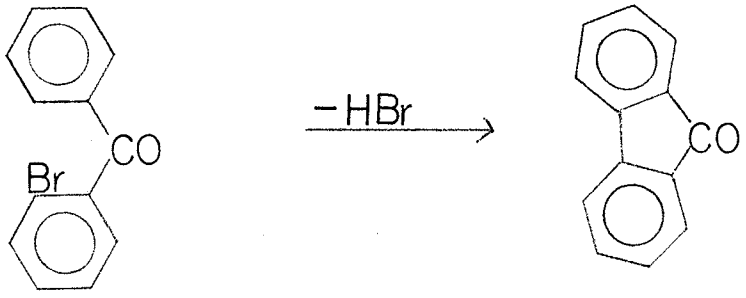

NO2
*CH2
[H]
NH2
*CH2
Ac2O
NHCOCH3
*CH2

chromatography and Infra Red analysis) were obtained. These biphenyl aldehydes were oxidised to acids, which on cyclisation gave fluorenones. They prepared several 2, 4-disubstituted fluorenones with different R and R^1.



(f) From 2-Substituted Benzophenones

Fluorenones may also be synthesized from o-halogen benzophenone derivatives.

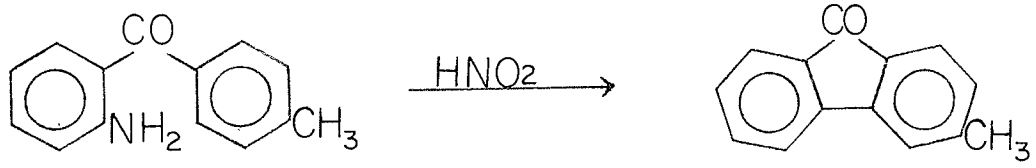


Montagne (57), (58) employed this method in the synthesis of several mono bromo- and dibromo derivatives of fluorenone. As Miller and Bachmann (54) have pointed out, this method possesses disadvantage in that the yields are small, the

intermediates are difficult to prepare, and rearrangement is possible because of the high temperature required to effect the elimination of halogen acid.

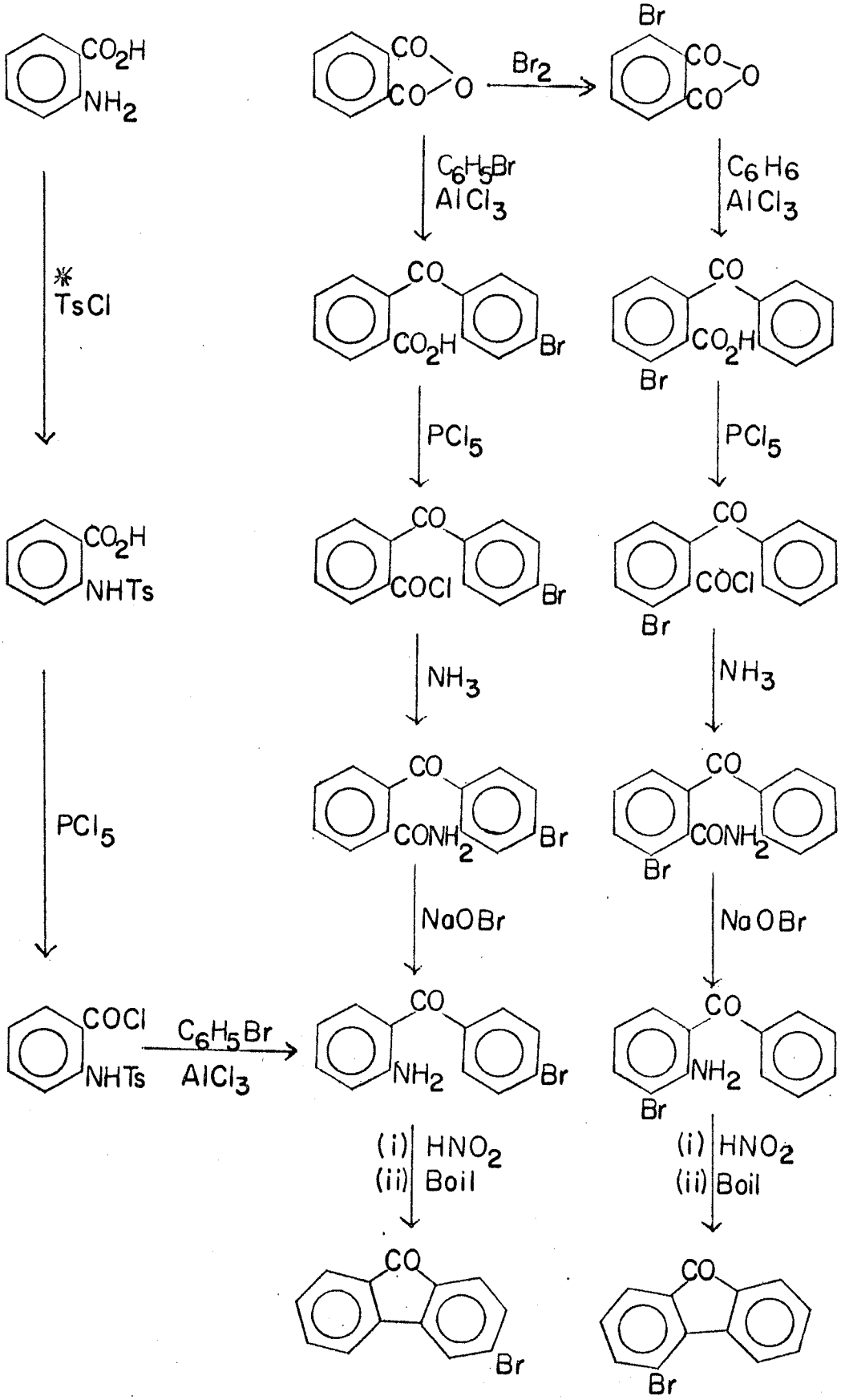
A few years later, it has been shown (11) that diaryl ketones with an ortho chlorine atom could be ring closed by heating with alkali in the presence of cupric oxide in a rotating iron bomb, to give the corresponding fluorenones in fairly good yields. Further studies on this reaction indicated that metallic iron was necessary for the formation of fluorenones. It can be added as a powder or the reaction can be conducted in an iron bomb.

A method somewhat similar to the preceding one, consists of the successive diazotization and internal coupling of derivatives of o-amino benzophenone. Ullmann and Mallet (72) prepared 3-methyl fluorenone by the action of nitrous acid on o-amino-phenyl-p-tolyl ketone.



This method has been widely used because of the yield, cost and generality of its application. For example, Miller and Bachmann (54) used this method to prepare 3- and 4-bromo fluorenones, starting from readily available chemicals, with satisfactory yields. Their work is as shown on the following page.

The mechanism of this cyclisation (known as Pschorr

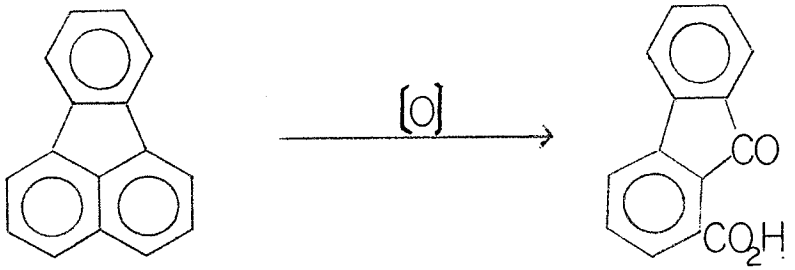


* TsCl:— P-$CH_3 \cdot C_6H_4SO_2Cl$

cyclisation) has been the subject of much debate. Recently, Abramovitch and Tertzakian (1) presented a thorough study of the mechanism in terms of modern concepts (like diradical cation etc.).

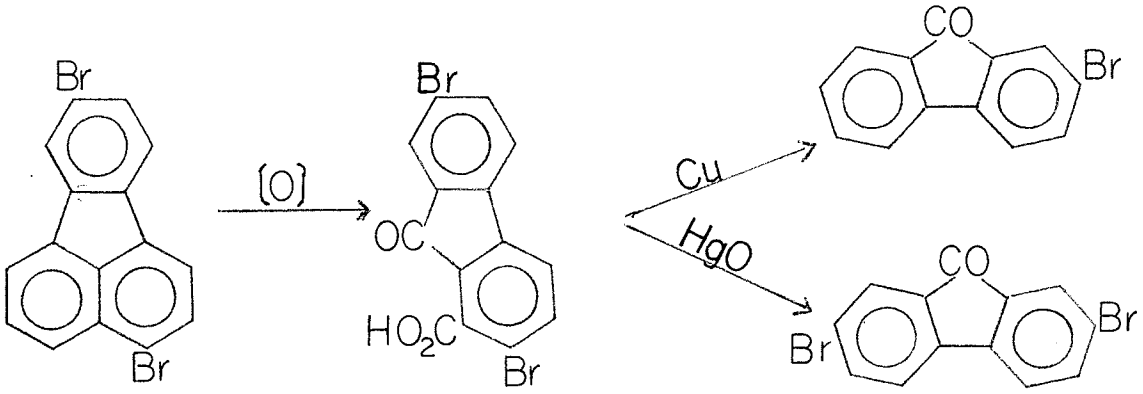
(g) From Fluoranthenes

The hydrocarbon fluoranthene offers another road to the synthesis of fluorenone derivatives. Fittig and Gebhard (28), (29) and Fittig and Liepmann (30) showed that the oxidation of fluoranthene with chromic acid yielded fluorenone-1-carboxylic acid with some fluoranthene-quinone.



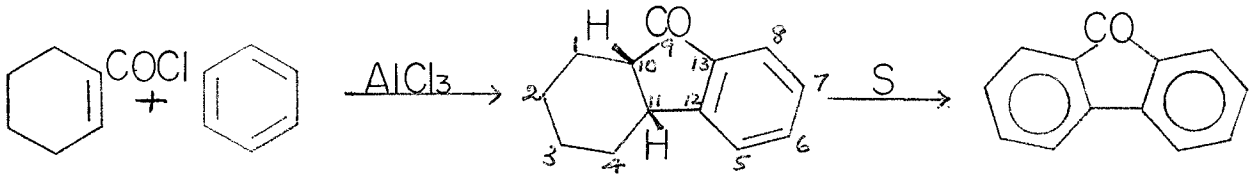
Fieser and Seligmann (26) in their work on carcinogenic compounds have confirmed this result. The development in the chemistry of fluoranthene in the past few years had a definite effect upon the advancement of fluorenone chemistry, for several substituted fluorenones have been obtained by the oxidation of substituted fluoranthenes followed by decarboxylation of the fluorenone-1-carboxylic acids.

For example, Campbell et al (12) in their study of the orientation of di-substituted fluoranthenes prepared 2-Bromo and 2, 7-dibromo fluorenones from 3, 8-dibromo fluoranthene.



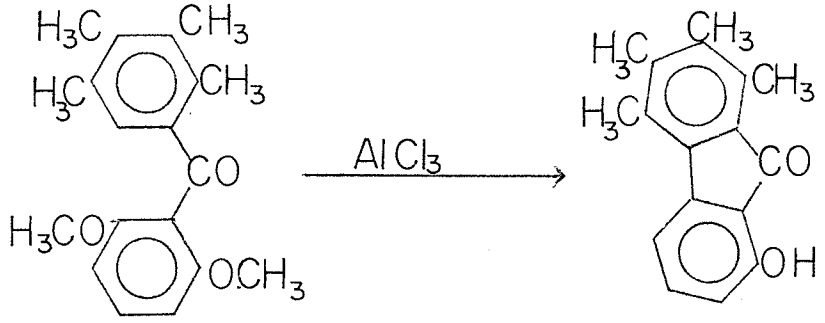
(h) From Miscellaneous Compounds

Colonge and Daunis (16) reported that the condensation of cyclohexene-1-carbonyl chloride with benzene, in the presence of aluminium chloride gave 1, 2, 3, 4, 10, 11-hexahydro fluorenone as a trans-isomer. Dehydrogenation of the hexahydrofluorenone with sulphur gave fluorenone. They also prepared several methyl substituted fluorenones by condensing cyclohexene-1-carbonyl chloride with toluene, p-xylene and m-xylene.

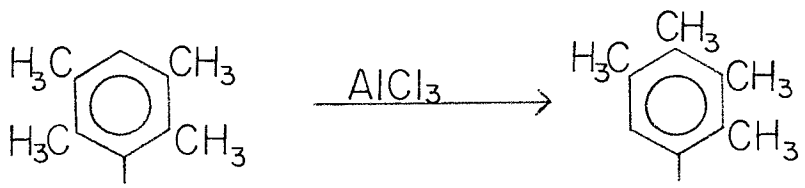


In 1962, Fuson, Bollero and Heins (34) reported that when the dimethyl ether of 2-Duroyl resorcinol was demethylated with hydrobromic acid or aluminium chloride, the phenol may undergo further reaction. With hydrobromic acid in fact, it suffered cleavage to resorcinol and duroic acid. Production

of phenol had been accomplished with aluminium chloride, but long heating with this reagent brought about the change to 1, 2, 3, 4-tetra-methyl-8-hydroxy fluorenone.



The isomerisation of duryl radical to the corresponding prehnityl group had been observed earlier.



Duryl Group Prehnityl Group

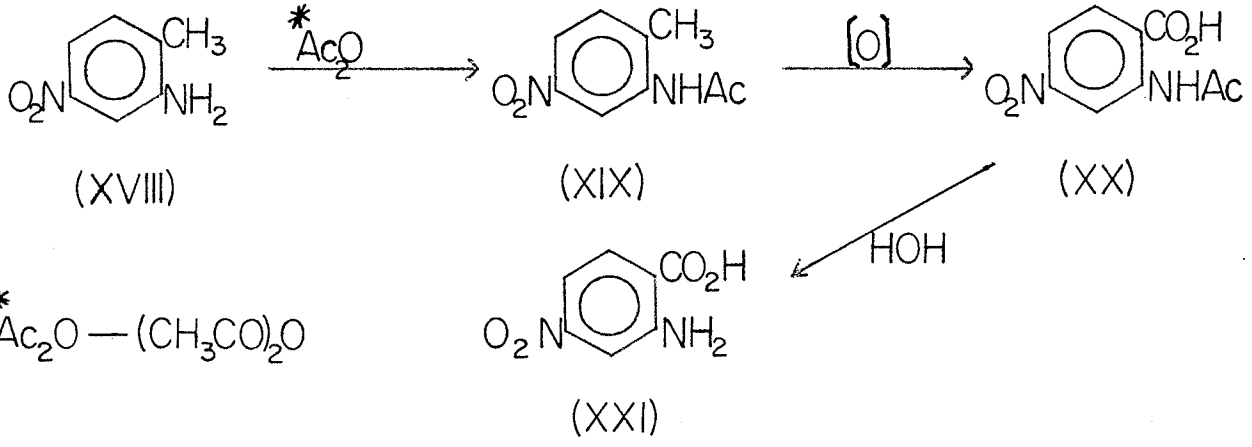
Therefore, one would expect the formation of the fluorenone to involve isomerisation followed by ring closure. The ring closure, thus made possible, is remarkable in that it is an arylation of an aromatic ring by a phenol. The structure of the new fluorenone was established by an independent synthesis of its methyl ether.

DISCUSSION OF RESULTS

In the present work, the synthesis of 3-bromo-6-nitro-fluorenone was investigated according to two schemes, which were based on previously recorded methods of fluorenone syntheses. The first scheme was not successful, however, the second scheme gave the bromo-nitro fluorenone in satisfactory yields. Of the various synthetic methods listed in the literature survey, the cyclisation of 2-amino benzophenones to fluorenones was chosen, as this method was known to give reasonably pure products with satisfactory yields.

Scheme I: Attempted synthesis of 3-bromo-6-nitro fluorenone starting from 4-nitro-anthranilic acid

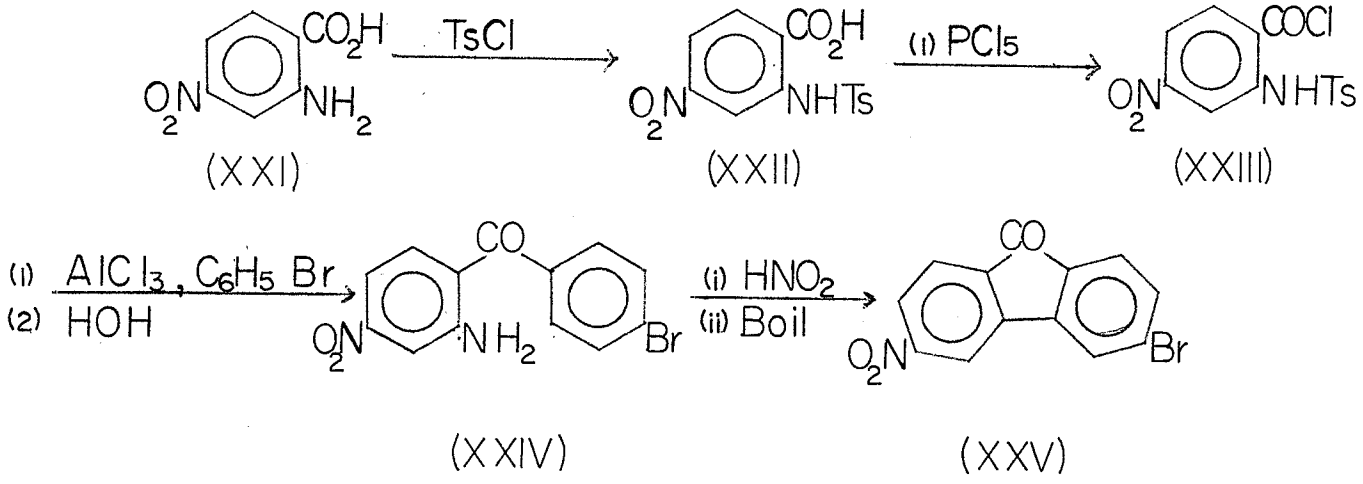
In this synthesis the sequence of reactions proposed was similar to that used by Miller and Bachmann (54) for the synthesis of 3-bromo fluorenone starting from anthranilic acid. 4-Nitro anthranilic acid was used as the starting material and it was prepared according to the directions described by Prysiasnuik (66).



(XVIII) (XIX) (XX) (XXI)

*Ac_2O — $(CH_3CO)_2O$

2-Amino-4-nitro toluene (XVIII) was first acetylated in order to protect the amino group. The acetylated product (XIX) was then oxidised to 2-acetamido-4-nitro benzoic acid (XX). This oxidation was carried out in an aqueous solution of potassium permanganate with magnesium sulphate. Magnesium sulphate was used as a buffer, to prevent the hydrolysis of the acetamido group to the amino group during oxidation. The 4-nitro anthranilic acid (XXI) was obtained by the hydrolysis of (XX). The synthesis of 3-bromo-6-nitro fluorenone was as attempted according to the following scheme.

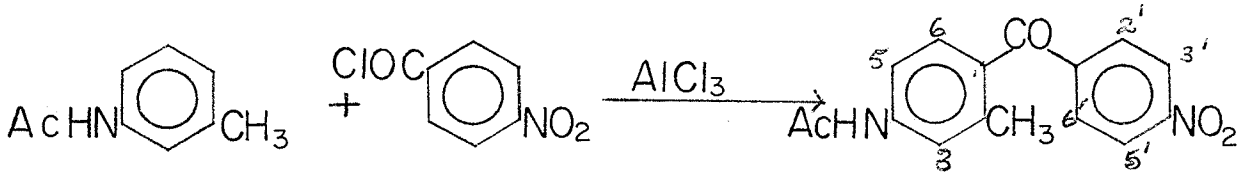


4-Nitro anthranilic acid (XXI), was tosylated to the tosyl anthranilic acid (XXII). The tosyl derivative was then converted to the acid chloride (XXIII) which was subjected to Friedel-Crafts conditions in bromobenzene. The tosyl group was used in this synthesis for two reasons; firstly, to protect the amino group of the nitro anthranilic acid; secondly, to effect para-substitution predominantly on bromo-

benzene. A study of the literature indicated that in most of the Friedel-Crafts reactions carried out so far, with the tosyl group (15), the para-substituted product was obtained exclusively. The Ortho-substitution was made difficult because of the steric effects induced by the bulky tosyl group. On the other hand, the use of the tosyl group presented a disadvantage in that strong hydrolytic conditions had to be used for its removal. Sometimes the hydrolysing reagents degraded the substrate giving tarry products. In this attempted Friedel-Crafts reaction several hydrolysing agents were used. All these failed to give the expected product. Concentrated sulphuric acid gave an unworkable tar, whereas concentrated hydrochloric acid failed to give a satisfactory product. This synthetic scheme was abandoned, because a satisfactory product was not obtained from the Friedel-Crafts reaction.

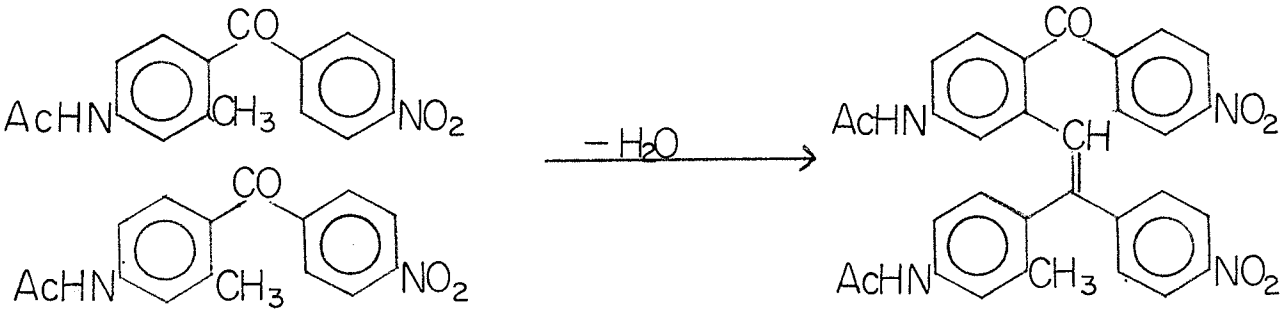
Scheme II: Synthesis of 3-bromo-6-nitro-fluorenone from m-acetotoluidide and p-nitrobenzoyl chloride

The failure of scheme I was attributed to the failure of the Friedel-Crafts reaction. So in this scheme it was decided to formulate a sequence of reactions leading to the bromo-nitro fluorenone, through well established Friedel-Crafts reactions. Mehta, Sacha and Patel (53) in a study of the Friedel-Crafts acylation of substituted anilides showed that m-acetotoluidide, when heated with p-nitrobenzoyl chloride and anhydrous aluminium chloride gave 4-acetamido-2-methyl-4-nitro benzophenone (XXVI).



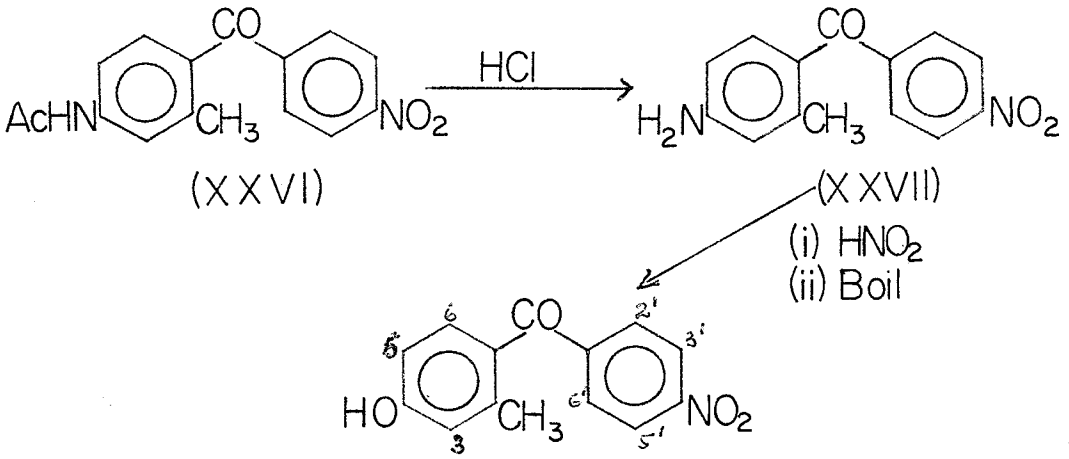
(XXVI)

They observed that it was necessary to use excess aluminium chloride to cut down the side reactions. The anilide, the acyl chloride and anhydrous aluminium chloride were used in the ratio 1:1:3 (by weight) respectively. A study of the literature indicated that the most predominant side reaction was the intermolecular condensation of the methyl group with the carbonyl group of the benzephenone as shown. A "dypnone" type of product would be obtained.

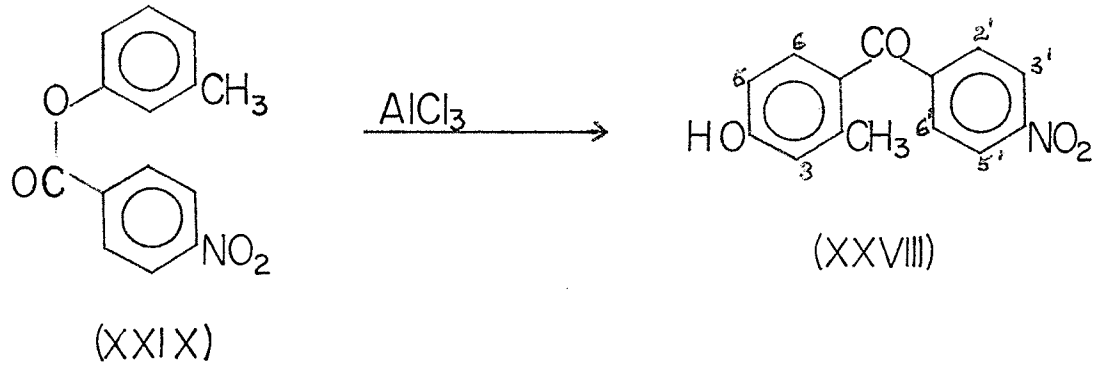


It has been suggested that excess aluminium chloride forms a complex with the carbonyl group of the benzophenone, thereby prevents such condensations described above. In the main Friedel-Crafts reaction substitution occurred para- to the acetamido group. The orientation of the benzophenone (XXVI)

was confirmed (53) in the following manner.



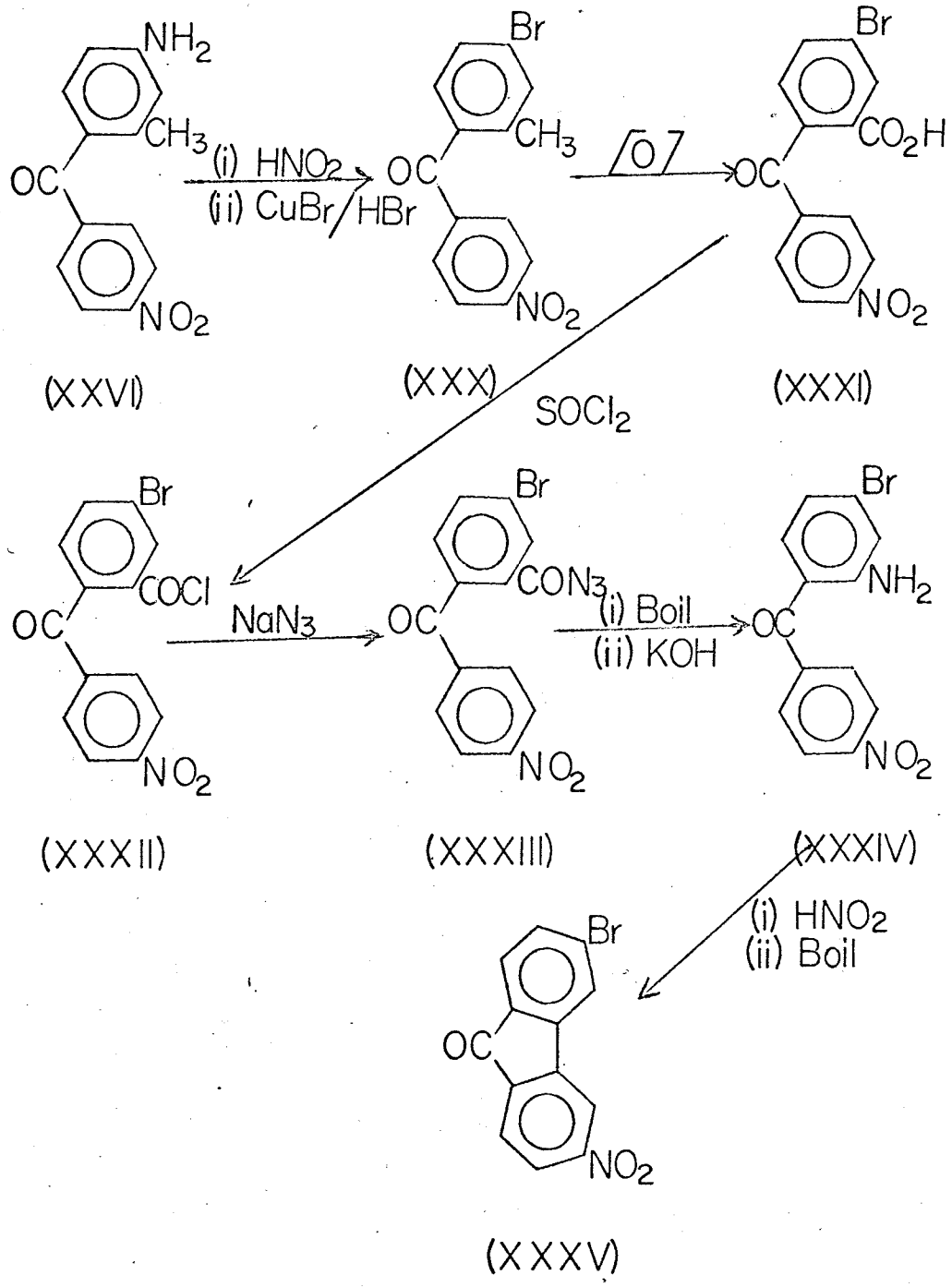
The acetamido group of the benzophenone (XXVI) was first hydrolysed to the amino group to give (XXVII), which was diazotised and boiled to give the hydroxy-methyl-nitro benzophenone (XXVIII). This benzophenone (XXVIII) was shown to be identical with known authentic sample of 4-hydroxy-2-methyl-4'-nitro benzophenone, obtained from the Fries re-arrangement of m-cresyl-p-nitro benzoate (XXIX).



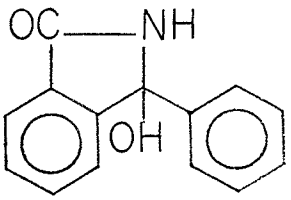
Thus, the orientation of the Friedel-Crafts product (XXVI) would be 4-acetamido-2-methy-4'-nitro benzophenone.

The synthesis of 3-bromo-6-nitro-fluorenone was carried out according to the scheme on the following page, starting with 4-amino-2-methyl-4'-nitro benzophenone (XXVII), the hydrolysis product of (XXVI). The amino ketone (XXVI) was obtained as orange red prisms after recrystallization from benzene. The amino ketone (XXVI) was converted to the bromo-ketone (XXX) and the methyl group in (XXX) was oxidised to the carboxylic acid (XXXI). The acid chloride (XXXII) obtained from the acid (XXXI) was converted to the amine (XXXIV) by the Curtius degradation. This degradation was carried out by the "Wet procedure" as described in Organic reactions (Vol. 3., p. 387). In this procedure, the intermediate products (acid azide, and isocyanate) were isolated from the reaction mixture, in order to prevent any side reactions taking place. The amine (XXXIV) so obtained, was diazotised and cyclised to give the 3-bromo-6-nitro fluorenone (XXXV).

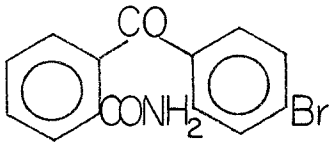
Before the Curtius degradation was tried, the conversion of the acid (XXXI) to the amine was attempted through the Hofmann degradation. In this attempted reaction, the acid was converted to the amide and the amide was treated with sodium hypobromite in sodium hydroxide. The expected product (XXXIV) was not obtained, instead an acidic compound was isolated. In another attempt, sodium hypochlorite was substituted for sodium hypobromite, an acidic product identical


NH2
CH3
OC
NO2
(i) HNO2
(ii) CuBr/HBr
Br
CH3
OC
NO2
[O]
Br
CO2H
OC
NO2
(XXVI)
(XXX)
(XXXI)
SOCl2
Br
COCl
OC
NO2
NaN3
Br
CON3
OC
NO2
(i) Boil
(ii) KOH
Br
NH2
OC
NO2
(XXXII)
(XXXIII)
(XXXIV)
(i) HNO2
(ii) Boil
Br
OC
NO2
(XXXV)

to that isolated earlier, was obtained. These side reactions leading to these acidic products might be attributed to the structural differences in the amide molecule. In 1964, Bhatt (10) suggested a pseudo amide structure (XXXVIa) for 2-[p-bromobenzoyl]- benzamide based on Infra-red spectral studies. Earlier, it was believed that this amide had an open structure (XXXVIb) as suggested by Miller and Bachmann (54).

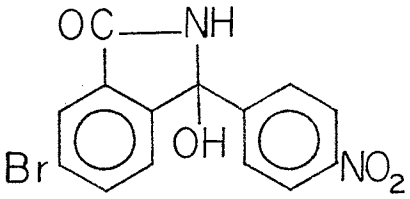


(XXXVIa)

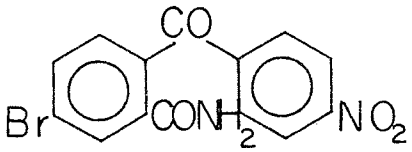


(XXXVIb)

In the present work an attempt was made to clarify the structure of 4-bromo-2-[p-nitrobenzoyl]- benzamide (XXXVII). The infra-red spectra of the amide tend to support both the structures (XXXVIIa) and (XXXVIIb).



(XXXVIIa)



(XXXVIIb)

Because of the solubility limitation, (the amide being insoluble in the required solvents), the nuclear magnetic resonance spectroscopy could not be used to confirm this fact. In the present stage, there are three possibilities for the structure; namely,

(i) the pseudoamide structure (XXXVIIa).

(ii) the open structure (XXXVIIb).

(iii) a tautomeric equilibrium between the forms (XXXVIIa) and (XXXVIIb).

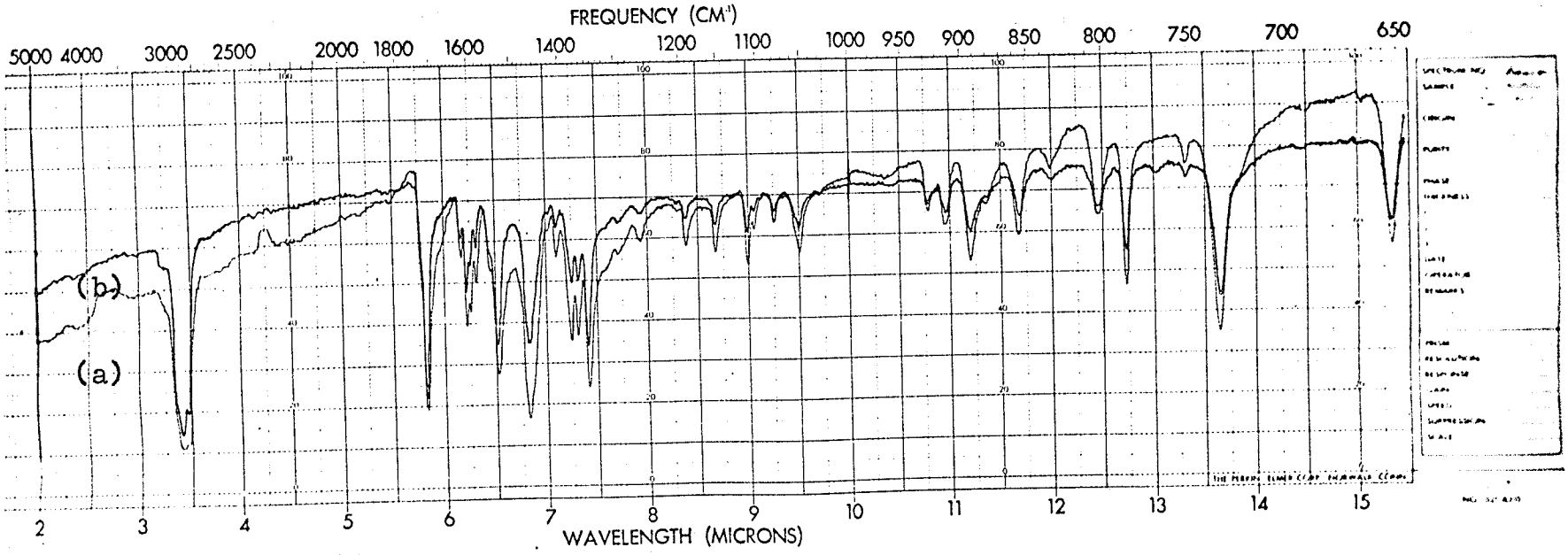
Perhaps an isotopic tracer study (see recommendations for future work on page63) on the molecule might reveal some information as to its structure. A careful study of the structure of the amide would be desirable, in order to identify the acidic product obtained in the Hofmann reaction.

The 3-bromo-6-nitro fluorenone (XXXV) melted at 339-341°C and was characterized by preparing the oxime (XXXVIII) [m.p. - 269-270°C]. The bromo-nitrofluorenone (III) obtained by Dolenko (20) melted at 329-330°C. However, the infra-red spectra of the bromo-nitrofluorenones (III) and (XXXV) indicated the identity of these compounds [see next page for the infra-red spectra of (III) and (XXXV)]. Analytical data for (III) and (XXXV) revealed that the product (III) obtained by Dolenko was impure and that the product (XXXV) synthesized in the present work was pure.

Analytical Data

Compound (III)	Calculated:	N = 4.61, Br = 26.28
	Found:	N = 4.34, Br = 23.39
Compound (XXXV)	Calculated:	N = 4.61, Br = 26.28
	Found:	N = 4.72, Br = 26.16

As expected, the impure compound (III) melted at a lower temperature. Furthermore, the impure specimen of (III) would be anticipated because the copper powder catalyst used



(a) I.R. Spectra of 3-bromo-6-nitro fluorenone (XXXV).

(b) I.R. Spectra of the bromo-nitrofluorenone (III).

Phase: Nujol Mull

(20) in the decarboxylation of the 3-bromo-6-nitro fluorenone-1- carboxylic acid might have debrominated a part of the product, leading to a low bromine content in the product [see the bromine analysis for (III)].

EXPERIMENTAL

(1) Attempted Synthesis of 3-bromo-6-nitrofluorenone from 4-nitro anthranilic acid

(a) Preparation of 2-acetamido-4-nitro toluene (XIX)

In a 500 ml. three necked flask equipped with a condenser and stirrer was placed 2-amino-4-nitro toluene (XVIII), (50 g, 0.33 mole) and acetic anhydride (138 g, 1.35 mole). The mixture was refluxed for two hours. Water was added cautiously to the hot solution and then the solution was boiled for several minutes to destroy the excess acetic anhydride. Dilution of this solution with water yielded crude 2-acetamido-4-nitro toluene (44 g). The product after recrystallization from ethanol melted at 148-150°C. Prysiasnuik (66) reported 149-150°C as the melting point of (XIX).

(b) Preparation of 2-acetamido-4-nitrobenzoic acid (XX)

This was carried out by treating 2-acetamido-4-nitro toluene (XIX) (10 g, 0.051 mole) in water (3 litres) at 95°C with potassium permanganate (25 g) in the presence of magnesium sulphate (12 g) and allowing the solution to remain at 90°C overnight. The crude acid (7.5 g) which had separated on acidification was filtered off and was treated with hot sodium carbonate solution. Any insoluble material was filtered off. The filtrate on acidification yielded the acid (XX) which after recrystallization from water melted at 215-216°C. The yield was about 7 grms. (61%). Prysiasnuik

(66) reported 215-216°C as the melting point of (XX).

(c) Preparation of 4-nitro anthranilic acid (XXI)

The previously mentioned acetyl derivative (XX) (10 g, 0.044 mole) was heated with concentrated hydrochloric acid (120 ml.) and ethanol (30 ml.) for two hours on a water bath. The reaction mixture was cooled and was diluted with water. The orange-red precipitate formed, was filtered off and dried. The crude acid was treated with hot sodium hydroxide (10%) and the undissolved material was removed by filtration. The filtrate on acidification yielded the acid, which after recrystallization from ethanol melted at 263-264°C (with decomposition). The yield was 7.0 grms. (86.1%). Prysiasnuik (66) reported 263-264°C as the melting point.

(d) Preparation of 4-nitrotosyl anthranilic acid (XXII)

The method used, was essentially similar to that described by Scheifele and DeTar (68).

Technical grade sodium carbonate (52 g, 0.48 mole) was added to water (300 ml.) in a litre flask. While the mixture was warmed, 4-nitro anthranilic acid (36.2 g, 0.2 mole) was added in portions and the temperature was raised to 70°C to effect complete solution. The solution was allowed to cool to about 60°C, and technical p-toluene-sulphonyl chloride (46 g, 0.24 mole) was added in portions over a period of about 20 minutes. When all the p-toluene sulphonyl chloride has been added, the reaction mixture was maintained at 60-70°C for an additional 20 minutes.

The temperature was raised to about 85°C. Norit (2 g) was added cautiously and the solution was filtered by suction through a previously heated Buchner funnel.

In a 2-litre beaker equipped with a mechanical stirrer which can be operated above the liquid level to break the foam, were placed concentrated hydrochloric acid (50 ml.) and water (50 ml.). The filtrate obtained above was cooled to about 50°C and was added to the hydrochloric acid in small portions and at such a rate that the mixture did not foam over. If efficient stirring was used in the foam layer, this addition could be carried out in 5 minutes. The product was isolated by filtration through a Buchner funnel and was washed on the filter with dilute hydrochloric acid and then with water. The product was allowed to air dry for 15 hours and was recrystallized from ethanol in pale yellow plates. The yield was 50.7 grms. (75.5%). M.P. :- 225-226°C.

Analytical Data

Calculated for $C_{14}H_{12}O_6N_2S$; N = 8.33, S = 9.52

Found; N = 8.35, S = 9.46

(e) Attempted Preparation of 2-amino-4-nitro-4'-bromo benzophenone (XXIV)

In a one litre three necked flask equipped with a stirrer, a reflux condenser and a thermometer extending to the bottom of the flask was placed 4-nitro tosyl anthranilic acid (16.8 g, 0.05 mole). Bromobenzene (150 ml.) and phosphorus pentachloride (11.9 g, 0.057 mole) were added and the mixture was stirred and heated at about 50°C for

30 minutes. The solution was cooled to 20-25°C and anhydrous aluminium chloride (29.0 g, 2.2 moles) was added in portions. When the addition was complete, the dark mixture was heated with stirring at about 80-90°C for 8 hours. The mixture was cooled to room temperature and poured on a mixture of ice and concentrated hydrochloric acid. The bromobenzene was removed by steam distillation. The grainy, brown crude product was separated by filtration, washed thoroughly with dilute hydrochloric acid, with water, then with sodium carbonate solution (5%) (to remove the nitro anthranilic acid and the starting material), and finally with water. The product was sucked reasonably dry. The crude sulphonamide was dissolved in concentrated sulphuric acid (160 ml.) and the mixture was warmed on a steam bath for 30 minutes. The solution was cooled and diluted with ice water. An unworkable tarry product was obtained. In a second attempt concentrated hydrochloric acid was used for the hydrolysis of the sulphonamide. Again an unsatisfactory product was obtained.

(2) Synthesis of 3-bromo-6-nitrofluorenone from m-acetotoluidide and p-nitrobenzoyl chloride

(a) Preparation of 4-amino-2-methyl-4'-nitro benzophenone (XXVI)

The method used was similar to that used by Mehta, Sacha and Patel (53).

In a two litre three necked flask, equipped with a Herschberg stirrer, a reflux condenser with a calcium

chloride tube and a dropping funnel were placed anhydrous aluminium chloride (75 g) and dry carbon-disulphide (50 ml.). The suspension was cooled in ice and a solution of p-nitro-benzoyl chloride (25 g) in carbon-disulphide (100 ml.) was added slowly with stirring. Once the addition was complete the stirring was continued for another 15 minutes. At the end of this time, a solution of m-acetotoluidide (25 g) in carbon-disulphide (100 ml.) was added carefully with cooling. The mixture was allowed to stand for an hour and then refluxed on a water bath for 4 hours. It was cooled in ice and ice cold concentrated hydrochloric acid (200 ml.) was added carefully to liberate the ketone. Most of the carbon-disulphide was distilled off using a water bath and the residual solution was filtered to isolate the ketone. The ketone was recrystallized from ethyl alcohol and water. This ketone was hydrolysed with concentrated hydrochloric acid (100 ml.) on a water bath for 5-6 hours. The solution was cooled, and was made alkaline by the addition of sodium hydroxide (10%). The amino ketone was filtered and was recrystallized from benzene. The 4-amino-2-methyl-4'-nitro benzophenone was obtained as red elongated prisms, melting at 164-166°C. The yield was 20.3 grms. (58.8%). Mehta, Sacha and Patel (53) reported 159-161°C as the melting point. The constitution of this compound was confirmed by analysis.

Analytical Data

Calculated for $C_{14}H_{12}O_3N_2$; N = 10.93

Found; N = 10.98

(b) Preparation of 4-bromo-2-methyl-4'-nitro-benzophenone (XXX)

The above amino ketone (XXVI) (16 g, 0.063 mole) was dissolved in hot hydrobromic acid (48%, 75 ml.) and the solution was cooled to 0°C by adding ice to it. A solution of sodium nitrite (6.0 g) in water (30 ml.) was cooled to 0°C and added slowly to the white suspension of the amine hydrobromide with vigorous stirring. The colour of the suspension turned from white to brownish yellow as the diazonium salt was formed. Once the addition was complete, the diazonium salt solution was allowed to stand 15 minutes at 0°C and was added to boiling solution of cuprous bromide (92 g) in hydrobromic acid (48%, 200 ml.) at such a rate that the boiling was not stopped. It was observed that vigorous stirring was necessary to cut down the foaming. The solution was boiled for 30 minutes and diluted with water whereupon a light reddish white solid precipitated. The solid was filtered off, dried and extracted with excess benzene. The benzene extract was washed successively with sodium sulphite solution (5%) [to remove any excess nitrous acid] with sodium hydroxide (10%) [to remove the acidic components like HB] and finally with water. It was dried over calcium chloride and the benzene was removed by distillation. The 4-bromo-2-methyl-4'-nitro benzophenone (XXX) was obtained as pale yellow needles from aqueous acetone. The yield was 17.2 grms. (86.0%). M.P. :- 110-111°C.

Analytical Data

Calculated for $C_{14}H_{10}O_3NBr$; N = 4.36, Br = 24.96

Found; N = 4.27, Br = 25.10

(c) Preparation of 5-bromo-2-(p-nitrobenzoyl) benzoic acid (XXXI)

The previously obtained 4-bromo-2-methyl-4'-nitro benzophenone (XXX) (15.6 g, approx. 0.05 mole) was dissolved in glacial acetic acid (45 ml.) under a reflux. A solution of chromium trioxide (13.2 g) in a mixture of water (30 ml.), glacial acetic acid (45 ml.) and concentrated sulphuric acid (15 ml.) was added slowly from a dropping funnel at such a rate that the temperature of the reaction mixture remained just below the boiling point. The mixture was refluxed for 3 hours, and was poured into excess water. The precipitated solid was filtered off and washed with water until it was white. The solid was suspended in hot water and potassium hydroxide solution (10%) was added to dissolve as much solid as possible. The hot mixture was filtered through a sintered glass funnel and the filtrate was cooled and acidified with concentrated hydrochloric acid. The 5-bromo-2-(p-nitrobenzoyl) benzoic acid (XXXI) was obtained as a pale yellowish white powder melting at 194-196°C. The yield was 13.2 grms. (78%).

Analytical Data

Calculated for $C_{14}H_8O_5NBr$, N = 4.00, Br = 22.83

Found; N = 3.96, Br = 22.97

(d) Preparation of 5-bromo-2-(p-nitrobenzoyl)-benzoyl chloride (XXXII)

The 5-bromo-2-(p-nitrobenzoyl) benzoic acid (XXXI) (5.5 g) was placed in a flask fitted with a reflux condenser and a calcium chloride tube. Benzene (40 ml.) was added and the reaction mixture was made into a suspension by stirring. To this suspension was added thionyl chloride (10 ml.) and the reaction mixture was refluxed for one hour. Benzene and thionyl chloride were removed by vacuum distillation. The residue in the flask was washed with anhydrous ether and dried in a dessicator. The 5-bromo-2-(p-nitrobenzoyl) benzoyl chloride (XXXII) was obtained as a white amorphous powder melting at 124-126°C. The yield was 4.2 grms. (72.5%).

Analytical Data

Calculated for $C_{14}H_7O_4NClBr$, N = 3.80, Cl and Br = 31.30

Found; N = 3.68, Cl and Br = 31.28

(e) Preparation of 5-bromo-2-(p-nitrobenzoyl)-benzamide (XXXVI)

The method used was similar to that of Hewett et al (40).

The acid (XXXI) (11.0 g) was dissolved in dry chloroform (25 ml.) and after the addition of thionyl chloride (20 ml.) was warmed under a reflux on a water bath until the evolution of hydrogen chloride was complete. The solvent and excess of thionyl chloride were distilled off, the last traces being removed by distillation with dry benzene (20 ml.) in a vacuum, this treatment being repeated once. Without further purification the acid chloride was dissolved in dry benzene and slowly treated with ammonia solution

(density: 0.880, 100 ml.) with cooling. Considerable heat was developed and the whole set to pasty mass. The crude amide was filtered off and washed with water. It was purified by washing it twice with hot water and recrystallizing it from ethanol. The 5-bromo-2-(p-nitrobenzoyl) benzamide was obtained as a white powder melting at 239-240°C. The yield was 8.0 grms. (72.9%).

Analytical Data

Calculated for $C_{14}H_9O_4N_2Br$, N = 8.03, Br = 22.89

Found; N = 8.04, Br = 22.87

(f) Attempted Preparation of 2-amino-4-bromo-4'-nitrobenzophenone (XXXIV)

First Attempt

The previously obtained amide (XXXVI) (3.50 g, 0.01 mole) was dissolved in sodium hydroxide solution (15%, 15 ml.) and ethyl alcohol (10 ml.). The solution was cooled to 0°C in ice and bromine (0.5 ml.) was added with stirring. The solution was then warmed on a water bath to about 80°C for two hours and cooled. No precipitate was formed on dilution, however a yellow product was obtained on acidification with dilute hydrochloric acid. This acidic product was obtained as yellow plates by recrystallization from ethyl alcohol. It melted at 232-233°C and the yield was 3.0 grms.

Analytical Data

Calculated for $C_{13}H_9O_3N_2Br$, N = 8.73, Br = 24.89

Found; N = 7.99, Br = 23.31

This yellow compound depressed the melting point of 5-bromo-2-(p-nitrobenzoyl) benzamide (XXXVI). Further, it dissolved readily in sodium hydroxide whereas the amide (XXXVI) was sparingly soluble in sodium hydroxide.

Second Attempt

In the second attempt, a cold solution of sodium hypochlorite was used instead of a sodium hypobromite solution. A standard solution of sodium hypochlorite was prepared according to the method described by Magnien and Baltzly (52).

(i) Preparation of a Standard Hypochlorite Solution

In a distilling flask equipped with a dropping funnel was placed potassium permanganate (6.7 g). The side-arm of the flask was joined by a glass tube dipping below the surface of a solution containing sodium hydroxide (16 g, 0.4 mole), dissolved in water (110 ml.) and cracked ice, contained in a graduated cylinder. The cylinder in turn was surrounded by an ice bath. Concentrated hydrochloric acid (50 ml.) was admitted slowly through the dropping funnel so as to produce a slow stream of chlorine. When all the acid had been added, the contents of the flask were heated with a small flame until the reflux point was little below the junction with the side-arm. A pyrex wool plug below the side-arm served to prevent acid splashings from being carried over. The hypochlorite solution was then made up to 160 ml. Such solutions contain slightly over 0.1 mole of sodium hypochlorite and 0.2 mole of excess sodium hydroxide.

(ii) Preparation of the amino benzophenone (XXXIV)

The amide (XXXVI) (1.75 g, 0.005 mole) was treated with sodium hydroxide solution (10%, 10 ml.) and the suspension was cooled in ice. Cold sodium hypochlorite solution (2.5 ml.) was added slowly to the suspension and the reaction mixture was stirred vigorously for 15 minutes. The mixture was heated on a water bath for one hour, cooled and diluted with water. No precipitate was formed, but a yellow product was obtained on acidification. This product after recrystallization from ethanol melted at 232-234°C and it was shown to be identical with the product obtained in the first attempt by mixed melting point.

(g) Preparation of 2-amino-4-bromo-4'-nitro benzophenone (XXXIV) via the acid azide

(i) Activation of Sodium Azide

The commercially available (Matheson, Coleman and Bell Co. Ltd.) sodium azide was activated according to the procedure described in Organic Reactions (Vol. (III) page 382).

Pure sodium azide (20 g) was moistened with hydrazine hydrate (85%, 0.5-1.0 ml.) and ground in a mortar until homogeneous. After standing for twelve hours the material was dissolved in the minimum amount of hot water in a beaker. Excess acetone was added to the cooled solution and the mixture was allowed to stand for one hour. The precipitated sodium azide was collected, washed with acetone and dried

for a short time in vacuum; yield 13 grms.

Sodium azide thus activated begins to lose its activity after a day, but the activity can be regenerated at any time by dissolving the azide in water and reprecipitating it with acetone.

(ii) Preparation of the Acid Azide (XXXIII)

Activated sodium azide (0.75 g) was dissolved in water (2 ml.) and the solution was added to a chilled solution of the acid chloride (XXXII) (1.5 g) in acetone (20 ml.). The reaction mixture was stirred for 15 minutes. The precipitated solid was filtered off and dried in vacuum. The acid azide melted at 99-101°C. The yield was 1.5 grms. (98.3%).

(iii) Preparation of the Amino Benzophenone (XXXIV) from the Acid Azide

The dry acid azide (1.5 g) in benzene (25 ml.) was boiled for 2 hours and cooled. Potassium hydroxide solution (50%, 15 ml.) was added and the mixture was warmed (not boiled) on a water bath, whereupon a yellow solid separated. Benzene was removed by vacuum distillation and the suspension was cooled and filtered. The product was treated with hot concentrated hydrochloric acid and the hot acid solution was filtered through a sintered glass funnel. The filtrate after cooling, was made alkaline by adding sodium hydroxide solution (10%). The 5-bromo-2-(p-nitrobenzoyl) aniline crystallized from pyridine in bright yellow needles melting at 213-214°C. The yield was 1.2 grms. (93.4%).

Analytical Data

Calculated for $C_{13}H_9O_3N_2Br$, N = 8.73, Br = 24.89

Found; N = 8.71, Br = 24.42

(h) Preparation of 3-bromo-6-nitrofluorenone (XXXV)

The 5-bromo-2-(p-nitrobenzoyl) aniline (XXXIV) (0.8 g) was dissolved in concentrated sulphuric acid (2 ml.), and a few drops of water were added to the solution. The amine sulphate separated as a yellowish white suspension. The suspension was cooled to 0°C in an ice bath. An ice cold solution of sodium nitrite (0.2 g) in water was added slowly to the cooled suspension. When the addition had been completed, the mixture was allowed to stand for 15 minutes. The yellowish white amine sulphate first dissolved and the solid diazo compound was formed. The diazo compound on warming dissolved and gave a yellow product which was filtered, washed with sodium hydroxide solution (10%) and then with water. The dried 3-bromo-6-nitrofluorenone crystallized as bright yellow plates from nitrobenzene and melted at 339-341°C. The yield was 0.3 grms. (39.6%).

Analytical Data

Calculated for $C_{13}H_6O_3NBr$, N = 4.61, Br = 26.28

Found; N = 4.72, Br = 26.16

The sodium hydroxide washings mentioned above on acidification gave 0.26 grms. of pale yellow solid which was presumably 2-hydroxy-4-bromo-4'-nitrobenzophenone, a side product in this reaction. This product was obtained as

light yellow needles from aqueous ethanol and melted at 150-151°C.

Analytical Data

Calculated for $C_{13}H_8O_4NBr$, N = 4.35, Br = 24.81

Found; N = 4.55, Br = 24.89

(i) Preparation of 3-bromo-6-nitrofluorenone oxime (XXXVIII)

The oxime of 3-bromo-6-nitrofluorenone was obtained by refluxing the fluorenone with hydroxylamine hydrochloride in ethanol for two hours. The ethanol solution on cooling gave light yellow product. This product on recrystallization from ethanol melted at 269-270°C.

Analytical Data

Calculated for $C_{13}H_7O_3N_2Br$, N = 8.78, Br = 25.04

Found; N = 8.70, Br = 25.45

The 3-bromo-6-nitrofluorenone (XXXV) was shown to be identical with the bromo-nitrofluorenone (III) obtained by Dolenko (20) by infra-red spectra (see page 46), and by mixed melting point.

SUMMARY

(1) An unambiguous nuclear synthesis of 3-bromo-6-nitrofluorenone has been successfully accomplished.

(2) The identity of the bromo-nitrofluorenone (III) obtained by Dolenko (20) as 3-bromo-6-nitrofluorenone has been established. Thus the evidence that 2-nitrofluoranthene brominated in the 9-position has been confirmed.

(3) The conversion of the 5-bromo-2-(p-nitrobenzoyl) benzoic acid (XXXI) to 2-amino-4-bromo-4'-nitrobenzophenone (XXXIV) has been accomplished through the Curtius degradation with high yields.

(4) As a result of this investigation, nine new compounds have been prepared. They are as follows:

(i) 4-Nitro tosyl anthranilic acid.

(ii) 4-Bromo-2-methyl-4'-nitro benzophenone.

(iii) 5-Bromo-2-(p-nitrobenzoyl) benzoic acid.

(iv) 5-Bromo-2-(p-nitrobenzoyl) benzoyl chloride.

(v) 5-Bromo-2-(p-nitrobenzoyl) benzamide.

(vi) 2-Amino-4-bromo-4'-nitro benzophenone.

(vii) 3-Bromo-6-nitrofluorenone.

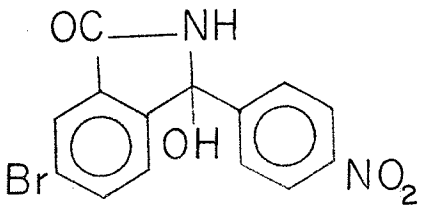
(viii) 3-Bromo-6-nitrofluorenone oxime.

(ix) 4-Bromo-2-hydroxy-4'-nitrobenzophenone.

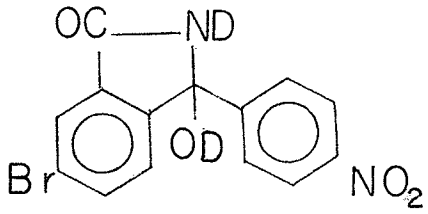
RECOMMENDATIONS FOR FUTURE WORK

(1) The scheme II (page 39) used in the synthesis of 3-bromo-6-nitrofluorenone could be applied as a general method for the synthesis of 3, 6-disubstituted fluorenones. The above scheme has an added advantage in that fluorenones with different functional groups in the 3 and 6- positions (i.e., unsymmetrical 3, 6-disubstituted fluorenones) could be synthesized. The amino group in 4-amino-2-methyl-4'-nitrobenzophenone (XXVI) could be converted to other important functional groups like fluoro, chloro, iodo, cyano, etc.). Further, the nitro group in the ketone (XXVI) could be reduced to the amino group which in turn could be converted to other important functional groups as mentioned above. Only very few 3, 6-disubstituted fluorenones are reported in the literature up to now. So a detailed study into the synthesis of 3, 6-disubstituted fluorenones could be attempted.

(2) It would be of interest, although not directly related to the project, to determine the structure of the acidic product isolated from the Hofmann reaction mixture of the amide (XXXVII). The structure of the amide could be attempted by studying the differences (if any) in the O-H and O-D absorptions of the normal amide (XXXVIIa) and the deuterated amide (XXXVIIc) in the near infra-red region of their spectrum.



(XXXVIIa)



(XXXVIIc)

The deuterated amide could be obtained from the acid chloride (XXXII) by treating it with deuterated ammonia (ND_3).

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