Glasgow University. Chemistry Department.

THE MECHANISM OF THE BENZILIC ACID RE-ARRANGEMENT.

A study of the benzilic acid re-arrangement by isotopic tracer techniques.

THESIS SUBMITTED FOR THE DEGREE OF Ph.D.

by

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Historical Survey of the Benzilic Acid Re-arrangement.

In I838 Liebig[I] heated benzil with alcoholic potash and obtained a clear solution which, on acidification with sulphuric acid, yielded crystals of an acid to which Liebig assigned the formula $C_{28}H_{22}O_5$. The experiment was repeated the following year by Zinin[2] who obtained the same product, to which he assigned the name "benzilic acid" and the formula $C_{28}H_{20}O_5$. Benzilic acid was again prepared by Limpricht and Schwanert[3] who carried out the reaction by heating benzil with alcoholic potash in sealed tubes. They assigned the formula $(C_6H_5)_2C(OH)COOH$ to the product, considering benzil to be the anhydride of this acid. Jena[4] showed that benzil was partly changed into benzilic acid on heating with water alone. Considering benzil again as the anhydride of benzilic acid he formulated the two substances as:-

Benzil $C(C_6H_5)2$ with $|\diagdown O$ and CO and Benzilic acid $C(C_6H_5)_2OH$ with $|$ and $CO.OH$

Grimaux[5] and Kekule[6], however, assigned the formula C_6H_5-C-OH with $|\diagdown O$ and C_6H_5-C-OH to benzilic acid, while

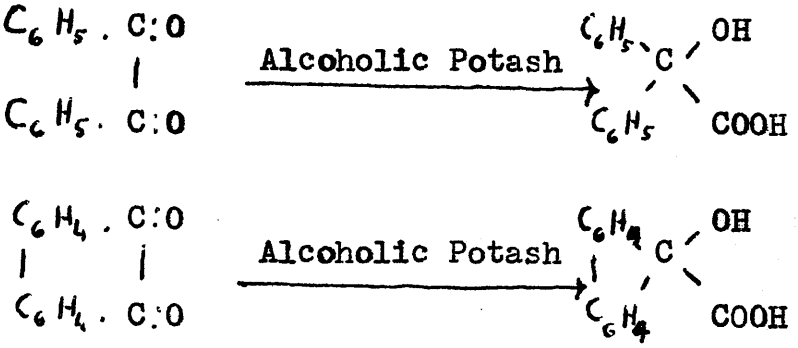
Oppenheim[7] and Städeler and Rossel[8] preferred the formula $C(C_6H_5)_2OH$
|
COOH

Finally both Symons and Zincke[9] and Radiszewski[10] decided on the now accepted formulae, benzil $C_6H_5CO.CO.C_6H_5$ and benzilic acid $(C_6H_5)_2\ C(OH)COOH$.

In both these latter papers the unusual nature of the change involved was remarked upon and interest was shown in the mechanism of such a change.

In the same year (1873), Graebe[11] had noticed that phenanthrenequinone dissolved to give a dirty-green product, on warming in alcoholic potash. This product on further warming, dissolved to give a reddish-brown solution which on prolonged boiling gave what Graebe thought to be phenanthrenehydroquinone. Caro, however, in an unpublished observation made to Baeyer, and referred to by the latter in a paper by Baeyer and Friedländer[12], pointed out that Graebe's solution, on acidification. gave a colourless crystalline solid, and that the product Graebe obtained was not the hydroquinone. Caro suggested that the acid obtained was fluorene-9-hydroxy-9-carboxylic-acid and compared the change involved with the benzil-benzilic acid transformation

to which it is formally analogous:-



Anschütz and Schultz[13] obtained the same product from phenanthrenequinone as did Graebe. They noticed that the product was liable to lose carbon dioxide on prolonged heating - this was the effect obtained by Graebe, and the product that to which he had applied the title phenanthrenehydroquinone.

The reaction was subsequently noticed also with various substituted benzils and phenanthrenequinones.

For example Fischer and Bösler[14] heated cuminil, pp'- di-isopropylbenzil, with alcoholic potash and obtained cuminilic acid, di-p-isopropyl benzilic acid:

Schmidt and Bauer[15], carried out the re-arrangement on the various substituted

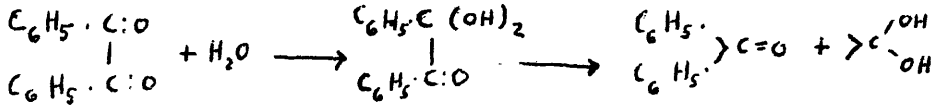
phenanthrenequinones such as 2-nitro-; 4-nitro; 2,7-dinitro-; 4,5-dinitro-; 2-bromo-; and 2-bromo-7-nitro-phenanthrenequinones and obtained the corresponding fluorene-hydroxy acids. They made the important observation that, whereas the unsubstituted quinone required warming to 80° in alcoholic potash to initiate the reaction, 2- and 4- mononitro-phenanthrenequinones began to re-arrange at 50° and in 10% alcoholic potash were completely converted after twenty minutes at 65°. Further, the 2,7- or 4,5- dinitrophenanthrene-quinones began to re-arrange at 15° and in 10% alcoholic potash were readily converted in ten minutes at room temperature. The 4,5- more readily re-arranged than the 2,7- dinitro compound. The reaction was also applied to the 2-bromo and 2,7-dibromo compounds, the presence of the bromine atom also being shown to facilitate the reaction.

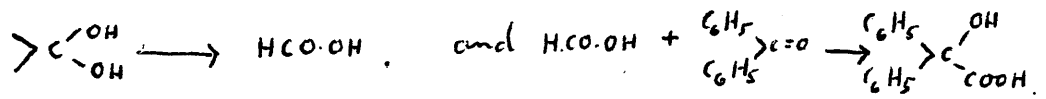
Meanwhile Staudinger[I6] had effected the benzilic acid re-arrangement using aqueous potash. H. Liebig[I7] repeated the experiment of Staudinger and showed that, by suitably controlling the temperature and time of the experiment, the re-arrangement was almost quantitative, lower yields on continued heating being due to decarboxylation

and air-oxidation to fluorenone- the product originally taken to be phenanthrenehydroquinone by Graebe.

The re-arrangement had continued to excite interest and various suggestions had been put forward as to the mechanism of the reaction.

J.U. Nef[18] suggested the following scheme:-





However benzophenone and formic acid under the conditions which favour the benzilic acid re-arrangement could not be made to condense to give benzilic acid.

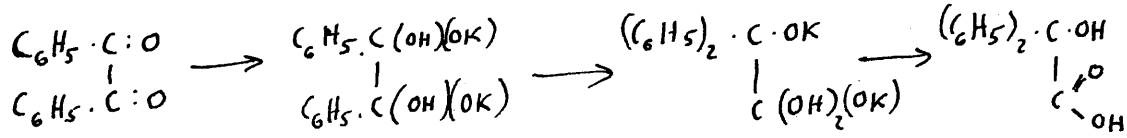
Schroeter[19] suggested a mechanism which involved the intermediate formation of diphenylketene and hydrogen peroxide, but Nicolet and Pelc[20] showed that these two reagents, under the conditions which favour the benzilic acid re-arrangement, do not condense to give benzilic acid.

A theory had been suggested by Tiffeneau[21] to cover the pinacol re-arrangement. This was based on unsaturated valencies produced by loss

of water, and it was adapted by Tiffeneau to cover the benzilic acid re-arrangement. The suggestion was that a molecule of alkali adds on to both carbonyl groups of the benzil, followed by elimination of water and isomerisation of the di-potassium-oxo-ethylene derivate thus formed to dipotassium benzilate.

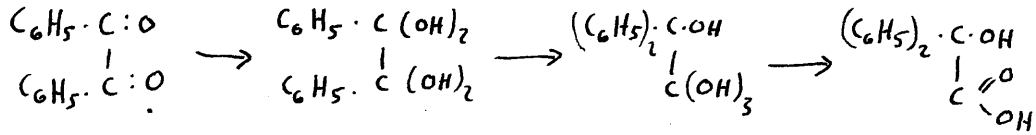
Michael[22] suggested that the transformation was due to the "great positive energy of the alkali", and suggested a scheme based on the preliminary addition of one molecule of potassium hydroxide to the benzil, followed by re-arrangement.

Staudinger and Binker[23] suggested a method involving addition of two molecules of potassium hydroxide to one of benzil:-



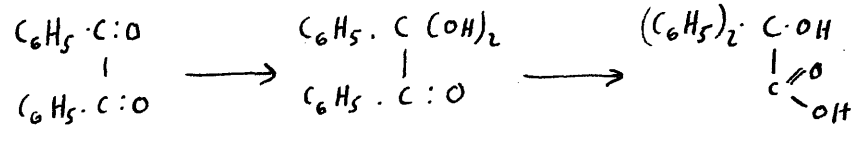
Lachman[24] showed that the re-arrangement occurs in water alone - (this had been first noticed by Jena in 1870 and also by Klinger[25] who had noticed that solutions of benzil, in moist ether and exposed to sunlight, slowly re-arranged to benzilic acid) - and suggested a scheme involving an internal

oxidation/reduction, for which he coined the name, "metakliny". He formulated the change then as:-



One hydroxyl group and one phenyl group on two neighbouring carbons at the benzil-dihydrate stage undergoing "metakliny".

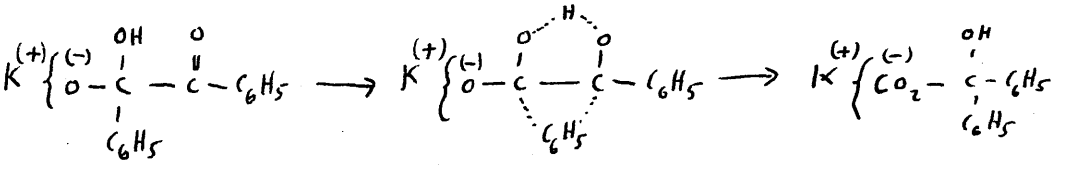
In the following year, Lachman[26] suggested that only one molecule takes part in the reaction. He showed that one molecule of benzil forms an additive compound with one molecule of sodium ethoxide. This additive compound decomposes with water to give benzil, sodium hydroxide, and alcohol; with ether it decomposes to give benzaldehyde and ethyl benzoate. He suggested a mobile hydroxyl group as the basis of the re-arrangement which he formulated as:-



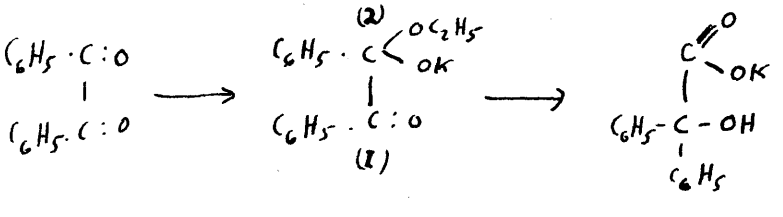
An hydroxyl and a phenyl group at the monohydrate stage undergoing "metakliny".

Scheuing[27] in the same year had obtained an

additive compound of benzil with potassium hydroxide which had the formula $C_{14}H_{10}O_2 \cdot KOH$, this with water, gave benzil and potassium hydroxide, but on warming to 80°, was rapidly converted into potassium benzilate.



Schonberg and Keller[28], using equimolecular proportions of benzil and potassium ethoxide in the absence of water, in an inert solvent, ether, obtained an 85% yield of benzilic acid. This supported schemes involving preliminary addition of alkali, and weighed against schemes involving more than one molecule of potassium ethoxide, e.g., that put forward by Tiffeneau. They suggested the following scheme:-



They pointed out that in the mono-alcoholate the carbon atom (1) is "valency undersatisfied", and carbon atom (2) is "valency oversatisfied", hence there is a strong tendency towards partial valency

between the carbonyl carbon (1), and the carbon of the phenyl group bound to the mono-alcoholate carbonyl carbon (2), and hence the tendency for the phenyl group to wander.

The following suggestions had thus been made:-

I. addition of one molecule of alkali.

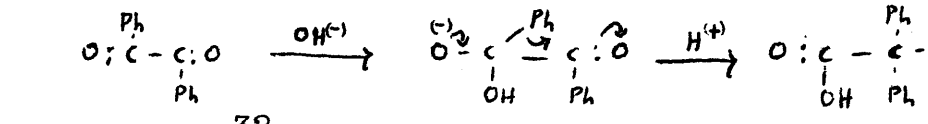
2. addition of two molecules of alkali.

3. addition of one molecule of water.

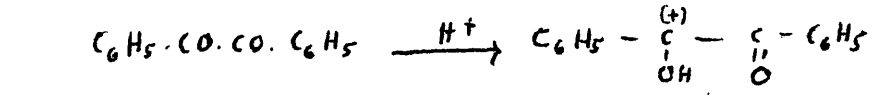
4. addition of two molecules of water.

The findings of Lachman, Jena etc. were against (I) and (2), these researchers having effected the rearrangement in the absence of alkali, and against (3) and (4) were the findings of Schönberg and Kellar, and also of Evans and Dehn[29], who had effected the reaction in an inert solvent in the absence of water.

In view of the above conflicting suggestions Ingold and Shoppee[30,31] suggested that the rearrangement was due to the addition of hydroxyl-ion followed by transformation of the ion so formed:-

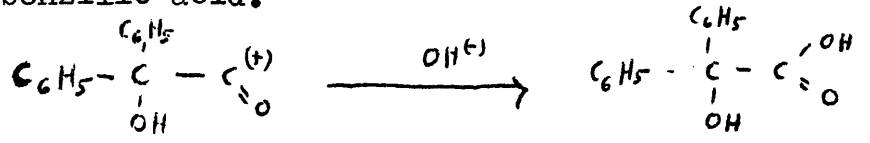


Whitmore[32] suggested that the change went via a positive ion and formulated the reaction thus:-



The carbon atom with the open sextet then attracts

the electron pair and phenyl group from the adjacent carbon atom, and addition of an hydroxyl group to the re-arranged fragment converts it then into benzilic acid.

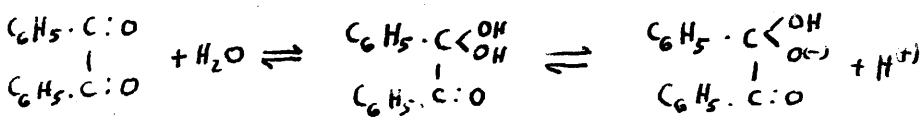


Ingold[33], however, points out that the change requires the presence of alkalis and is not catalysed by acids hence he prefers the negative ion as intermediate.

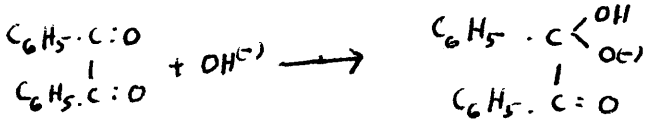
Also it may be noted here, referring back to Schmidt and Bauer's observations on nitrophenanthrene-quinones, that the reaction is facilitated in the presence of electro-negative groups, that this is the typical condition met with in Class B reactions involving attack by a negative ion. In Whitmore's scheme above, the rate-controlling step would be the attack by the hydrogen proton, and hence the re-arrangement ought to be facilitated by the presence of electro-positive groups.

In I936 Westheimer[34] investigated the kinetics of the transformation. He showed that the reaction was bimolecular, depending on the concentrations of both benzil and hydroxyl ions. The kinetic data favour the negative ion as the intermediate and Westheimer suggests that it could be formed in

three ways:-

(1) 

i.e. by removal of a proton from the benzil monohydrate.

(2) 

i.e. by addition of an hydroxyl ion to benzil.

(3) Direct ionisation of the hydrate.

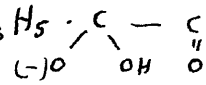
The kinetic data were against this last possibility. Against the first possibility we have the evidence of Evans and Dehn quoted above. Furthermore Westheimer produced evidence against any doubly ionised benzil molecule taking part. This leaves possibility (2) above, which involves direct addition of an hydroxyl ion to benzil.

Blanksma and Zaaiger[35] measured the rates of the reaction in methyl and ethyl alcohols and with sodium and potassium hydroxides. They showed that the reaction was slightly faster in methyl alcohol than in ethyl alcohol, and with sodium rather than potassium hydroxide. This is in agreement with an attack by an hydroxyl ion since the ionisation constant for sodium hydroxide, K_{NaOH}, is 0·038; and for potassium hydroxide, K_{KOH}, is 0·031.

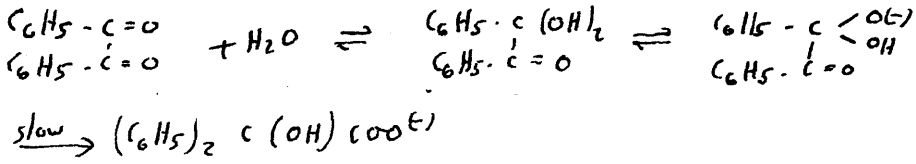
This was the position in I938. The availability of the radioactive isotopes of carbon, ^{II}C and ^{I4}C from I939 and I940 respectively made possible a new approach to problems in organic chemistry by the study of reaction mechanisms using isotopically differentiated samples. Furthermore, improved techniques for obtaining an enrichment of the naturally occurring ^{I3}C isotope, due to such workers as Clusius and Dickel[36] and Taylor, together with more convenient means of measuring concentrations of stable isotopes, due to Rittenberg[37] and particularly to Nier[38] and Graham[39], made the following of organic reactions by the use of stable, isotopically enriched, samples, feasible. Subsequent studies on the mechanism of the benzilic acid re-arrangement have all involved the use of isotopically differentiated samples.

The first of these investigations was made by Roberts and Urey[40], who carried out the reaction between benzil and water, which was isotopically enriched as regards the oxygen atom, using ^{I8}O. The reaction was conducted both in neutral and in alkaline solutions and Westheimer's results were considered in the light of the findings:-

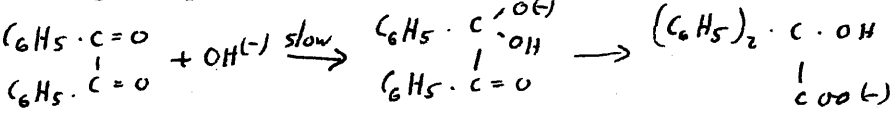
The reaction is I^{st} order with respect to both benzil and hydroxyl ion but does not exhibit general base

catalysis. This can be explained only on the assumption, originally made by Ingold, that the re-arrangement takes place through an intermediate ion of the formula:- 

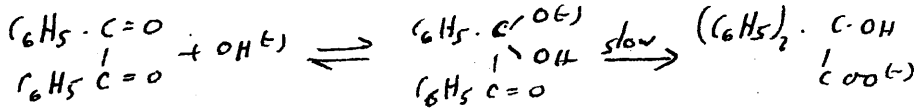
Three mechanisms which would all give the same rate equation, $-d(\text{benzil})/dt = K(\text{benzil})(OH)$ and which are therefore kinetically indistinguishable are possible, viz:-

1. 

i.e. formation of the monohydrate followed by fast reversible ionisation of the hydrate, followed by slow irreversible re-arrangement of the ion as the rate controlling step.

2. 

i.e. slow attack by the hydroxyl ion, followed by fast re-arrangement of the complex negative ion.

3. 

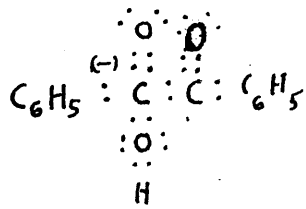
i.e. fast reversible attack by the hydroxyl ion followed by slow re-arrangement of the ion as the rate controlling step.

If benzil undergoes a rapid reversible hydration as in mechanism 1., it should rapidly exchange both its

oxygen atoms with the oxygen of the water. If mechanism (2) were correct, no change in the isotopic composition of the water should take place. If mechanism (3) were correct, the possibility of migration of a proton from one oxygen atom to the other in the complex negative ion, formed by addition of hydroxyl ion, will determine whether or not the benzil will exchange.

Roberts and Urey found that exchange took place, hence mechanism (2) can be eliminated at once. In neutral solution a slow change took place, in alkali solution complete exchange took place in four minutes, hence there is little doubt that reaction (3) is the most probable one.

According to Ingold, the true unstable intermediate is:-



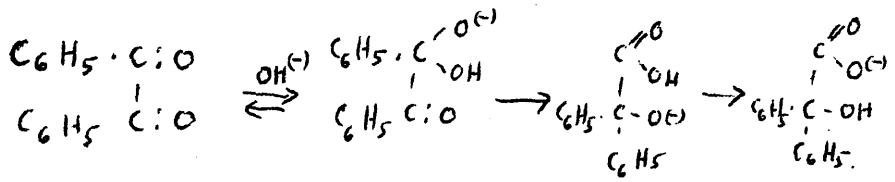
The carbon atom with ten electrons will tend to lose an electron pair - by loss either of:-

(1) $OH^{(-)}$ which would result in the reformation of benzil, this occurs rapidly hence the first stage in mechanism (3) given above, is rapid and reversible.

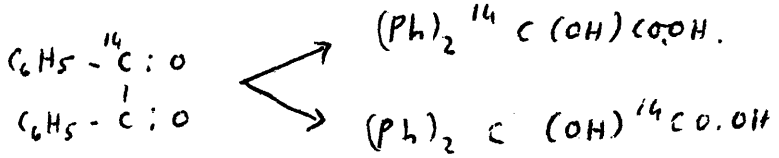
or

(2) $C_6H_5^{(-)}$ by a slower process, followed by addition of the $C_6H_5^{(-)}$ to the adjacent carbon atom which is an electron /

attracting centre. This is succeeded by rapid removal and addition of a proton to the appropriate oxygen atom.



Stevens and Attree[41] effected the benzilic acid transformation using benzil, which was isotopically enriched as regards ^{14}C at one of the carbonyl carbons:-



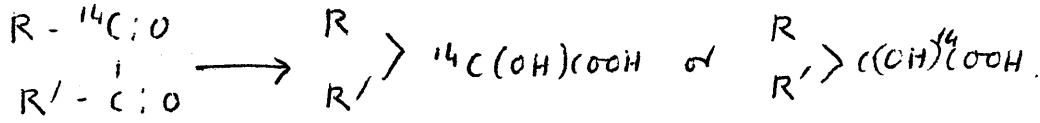
Oxidation of the hydroxy acid obtained to benzophenone and carbon dioxide and assay of the ^{14}C content of these, gave that the ratio of $(Ph)_2\ ^{14}C(OH)COOH$ to $(Ph)_2\ C(OH)^{14}COOH$ was $I \cdot II \pm 0 \cdot II$ i.e. that in $C_6H_5 - {}^{14}CO.CO-C_6H_5$ the $C_6H_5-{}^{12}C$ bond broke more readily than the $C_6H_5-{}^{14}C$ bond by about 10%. This is an example of the so-called "isotope effect". Since isotopes differ in mass and zero point energies, physicochemical differences between the bonds, e.g. $^{12}C-{}^{12}C$ and $^{12}C-{}^{13}C$ may be expected.

The isotope effect was first noticed by Beech[42] and his co-workers who found that the

dissociation probabilities of the $^{12}C-^{12}C$ and $^{12}C-^{13}C$ bonds, in the molecule-ions formed by electron impact on propane -I-^{13}C, differ by about 20%. Later, these workers carried out the thermal decomposition of propane -I-^{13}C and found that the frequency of rupture of the $^{12}C-^{12}C$ bond was 8% higher than the frequency of rupture of the $^{12}C - ^{13}C$ bond. Also Weigl and Calvin[44] noted a considerable isotope effect in a photosynthetic experiment and Yankwich and Calvin[45] noted an isotope effect amounting to 12% in the decarboxylation of malonic acid, isotopically enriched as regards ^{14}C at one of the carboxylic acid carbons, and amounting to 30% in the decarboxylation of bromomalonic acid, isotopically enriched at one of the carboxylic acid carbons. These large isotope effects were disquieting, as they would invalidate the use of carbon isotopes for following organic reaction mechanisms. However, they were brought into question by Bigeleisen[46] who calculated the isotope effect for the decarboxylation of labelled malonic acid and reached a figure which agreed well with the findings of Lindsay[47] and later with the findings of Bigeleisen[49] himself. The subsequent findings, particularly of Lindsay[48], have resulted in the acceptance

of a figure between about 2·5% - 3·0% as the isotope effect involved in the comparison of $^{12}C-^{12}C$ and $^{12}C-^{14}C$ bonds, the value being lower at higher temperatures. A figure is arrived at in the present research to ascertain that the results obtained are not invalidated by an isotope effect.

Further application of the use of isotopes to the investigation of the benzilic acid re-arrangement was made by Neville[50] who investigated the products of the re-arrangement of monocarbonyl-labelled asymmetrically substituted benzils.



R was the C_6H_5- group and R/ was H–, $C_6H_5CH_2-$, $pCH_3OC_6H_4-$ or p-Cl C_6H_4-

By oxidation of the hydroxy acid obtained to the corresponding substituted benzophenone and carbon dioxide and comparison of the activities of these, the relative rates of migration of the groups concerned could be given.

Compound	Percentage of Phenyl Group Migrating
$C_6H_5-^{14}CO.CO-H$	100%
$C_6H_5-^{14}CO.CO-CH_2.C_6H_5$	100%
$C_6H_5-^{14}CO.CO-C_6H_4.O.CH_3$	100%
$C_6H_5-^{14}CO.CO-C_6H_4.Cl$	39%

Roberts and Smith[51] carried out the re-arrangement on monocarbonyl-labelled p-methoxybenzil.

Two products are possible:-

1) $CH_3OC_6H_4.\ {}^{14}C{:}O$ / $C_6H_5.\ C{:}O$ $\longrightarrow$ C_6H_5 / $CH_3OC_6H_4$ $>{}^{14}C(OH)COOH$

2) $CH_3OC_6H_4.\ {}^{14}C{:}O$ / $C_6H_5.\ C{:}O$ $\longrightarrow$ C_6H_5 / $CH_3OC_6H_4$ $>C(OH){}^{14}COOH.$

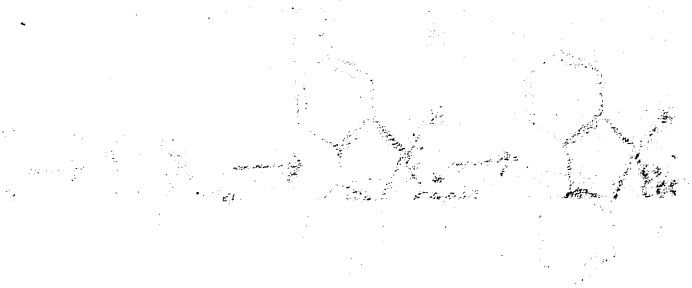
On mild oxidation of the resulting hydroxy acid, and measurement of the relative activities of the carbon dioxide and substituted benzophenone obtained, the relative ease of migration of the phenyl and p-methoxyphenyl groups can be calculated. The re-arrangement was carried out at various temperatures, the following results being obtained:-

Temperature at which re-arrangement carried out.	%age of Phenyl group migrating.
100°	65·5
70°	63·2
25°	68·5

These results show that the phenyl group migrates more readily than the p-methoxyphenyl, the percentage of phenyl migrating increasing with lower temperature but averaging about 65%.

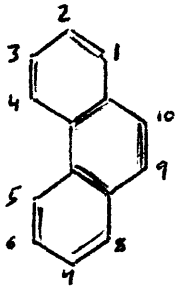
This result differs strikingly from the result

obtained by Neville, who, in a similar experiment found that phenyl migrated 100%. This will be discussed in the light of the results of the present investigation.

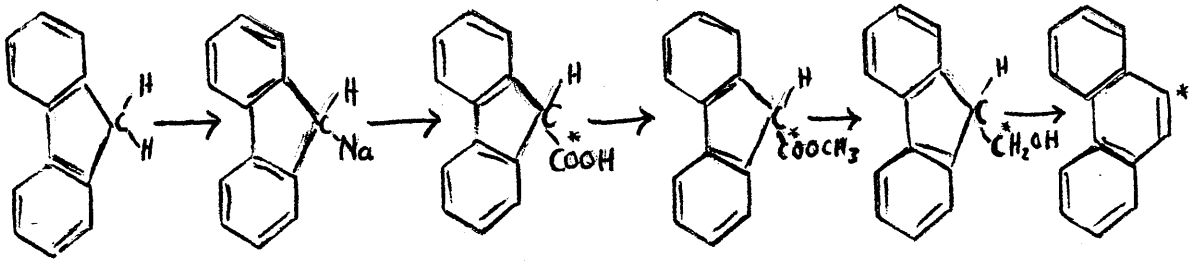


Scope and Nature of the Present Research.

It was decided to prepare various, asymmetrical, labelled α-diketones and to submit them to the benzilic acid re-arrangement. If a known ^{13}C ratio occurs across the carbonyl carbons of the diketones, then examination of the products of the re-arrangement for isotope distribution should give some information as regards the mechanism of the change.

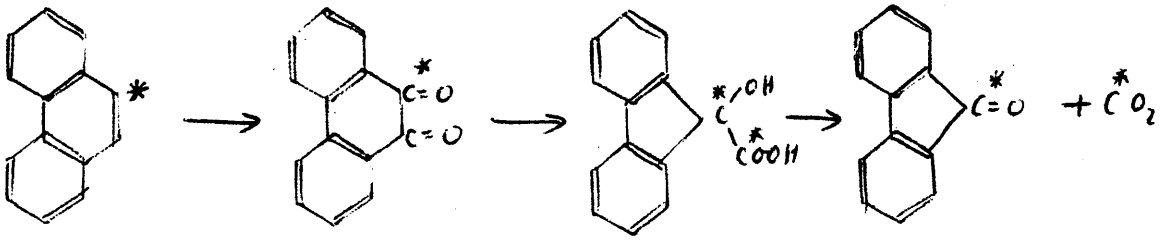


Phenanthrene has been prepared [52] labelled at the C_9 position with ^{14}C, by the following series of reactions starting with fluorene.



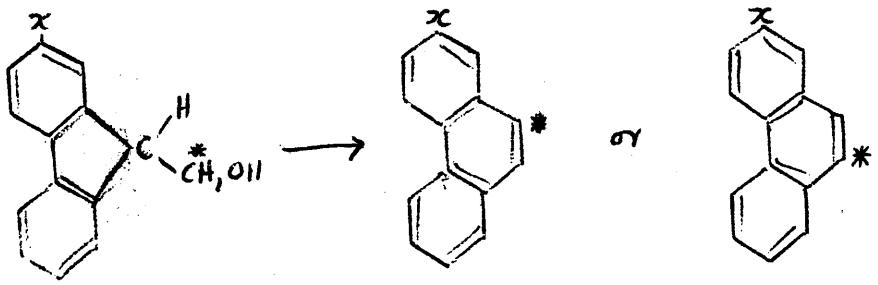
Oxidation of the phenanthrene would give phenanthrenequinone, which could then be submitted

to the benzilic acid re-arrangement.



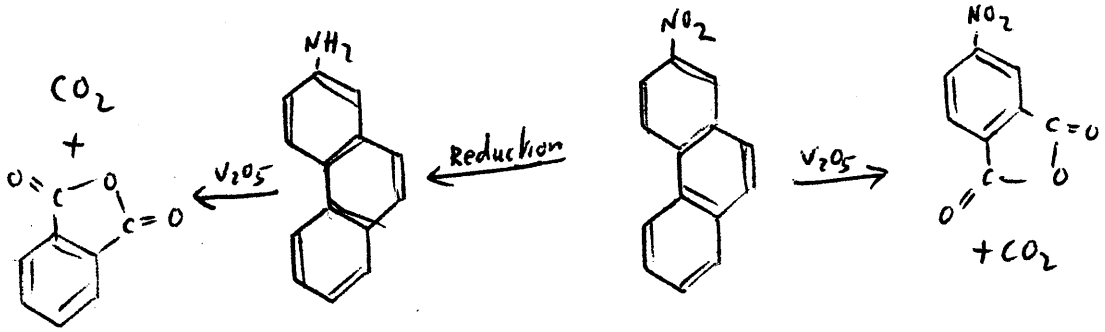
In the case of the non-substituted series beginning with fluorene, since the Wagner re-arrangement from the fluorene-9-carbinol to phenanthrene is irreversible the phenanthrene is presumably labelled uniquely at the 9- position. However, after the benzilic acid re-arrangement stage, since the phenanthrenequinone can split in two ways to give fluorene 9 - hydroxy - 9-carboxylic acid, this is presumably labelled both at the C_9 position and at the carboxylic acid carbon. Mild oxidation of the hydroxy-acid would give the corresponding ketone and a carbon dioxide sample which could be assayed for ^{13}C content. Oxidation of the ketone would give another carbon dioxide sample. Comparison of the two samples for isotope enrichment could then be made.

In the case where the fluorene-9-carbinol is asymmetrically substituted, ring enlargment could occur in two ways, viz:-



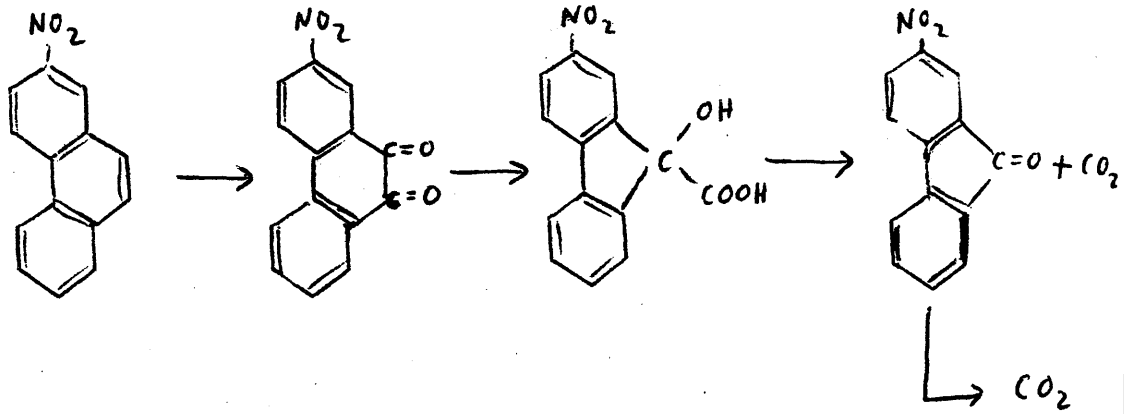
i.e. labelled at either the 9- or 10-positions. the actual result obtained would probably be a mixture of both products, the relative abundance depending on the mechanism of the ring enlargement and the nature and position of the substituent X.

Where X is the nitro- group, the relative abundances at positions 9- and 10-, with regard to ^{13}C, in the resulting 2 nitrophenanthrene, were thought to be obtainable by the following reactions. These are an adaptation of the well known system due to Graebe for the elucidation of the structure of naphthalene[53].



Oxidation of the 4-nitrophthalic anhydride and phthalic anhydride samples, obtained by the vanadium pentoxide oxidation of the 2-nitro and 2-amino phenanthrenes respectively, to carbon dioxide, and assay of the two carbon dioxide samples for ^{13}C enrichment, would then give the ^{13}C enrichment across positions 9- and 10- in the original 2-nitrophenanthrene.

A further sample of this 2-nitrophenanthrene could then be submitted to the standard sequence:-

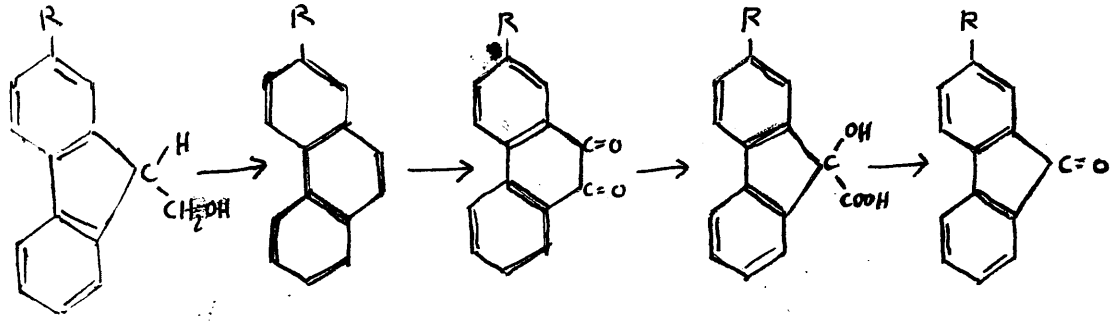


Investigation of the relative ^{13}C abundance of the two carbon dioxide samples and comparison with the known ^{13}C ratio across positions 9- and 10- in the 2-nitrophenanthrene would give the directive influence of the 2-nitro group in the re-arrangement.

Furthermore, from a further sample of the 2-nitrophenanthrene by standard diazotisation reactions, the various 2-halo and 2-methoxy and,

by straightforward reduction, 2-amino phenanthrenes would be available. These could then be oxidised to the quinones, re-arranged, and selectively oxidised as before to give the directive effects of the 2-chloro, 2-bromo, 2-iodo, 2-methoxy and 2-amino groups.

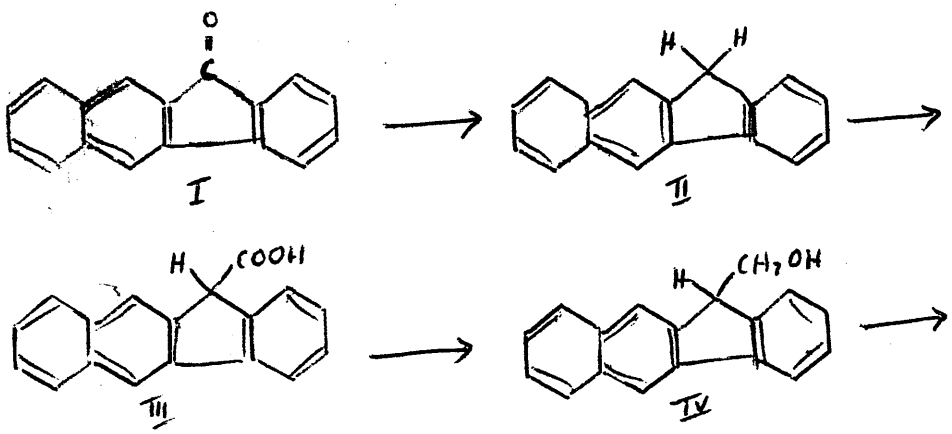
In the course of the work, interest was aroused in the mechanism of the Wagner re-arrangement involved in the ring-enlargement stage. Since the relative enrichments involved in the benzilic acid stage are already known from the previous stage of the research, on the 2-halo and 2-methoxy phenanthrenequinones, it was thought that, by preparing these same substituted phenanthrenes from the corresponding substituted fluorene - 9 - carbinols, and study of the ^{13}C enrichment, some information on the mechanism of the Wagner re-arrangement could be obtained.

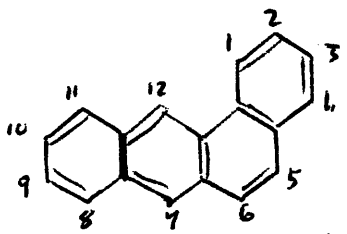


Where R is the nitro, methoxy, chloro, bromo, or iodo group, the effect of all these on the ring

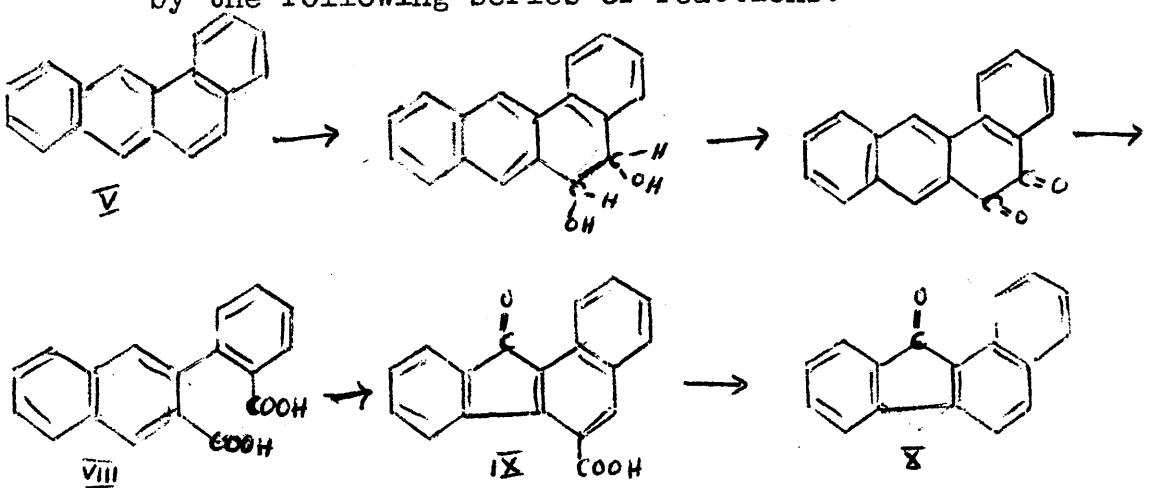
enlargement could be determined, and hence presumably a mechanism given.

Isotopic studies of the Wagner re-arrangement have been made by Collins, Burr and Hess[54] who carried out the following series of reactions, beginning with 2: 3 benz-fluorenone.



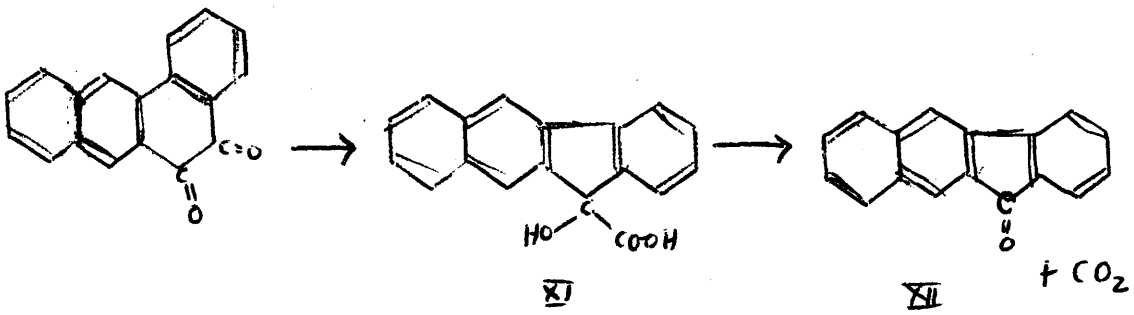


Collins, etc. obtained the ^{14}C distribution across positions 5- and 6- in the resulting benz(a)anthracene by the following series of reactions:-



Measurement of the activities of $\overline{IX}$ and $\overline{X}$ showed that in the benz(a)anthracene positions 5 and 6 were relatively enriched in the proportion of 48:52.

This was repeated in the course of the present work using ^{13}C and the quinone $\overline{VII}$, benz-(a)-anthracene 5-6 quinone, submitted to the benzilic acid re-arrangement as before.



$\overline{XI}$ $\overline{XII}$

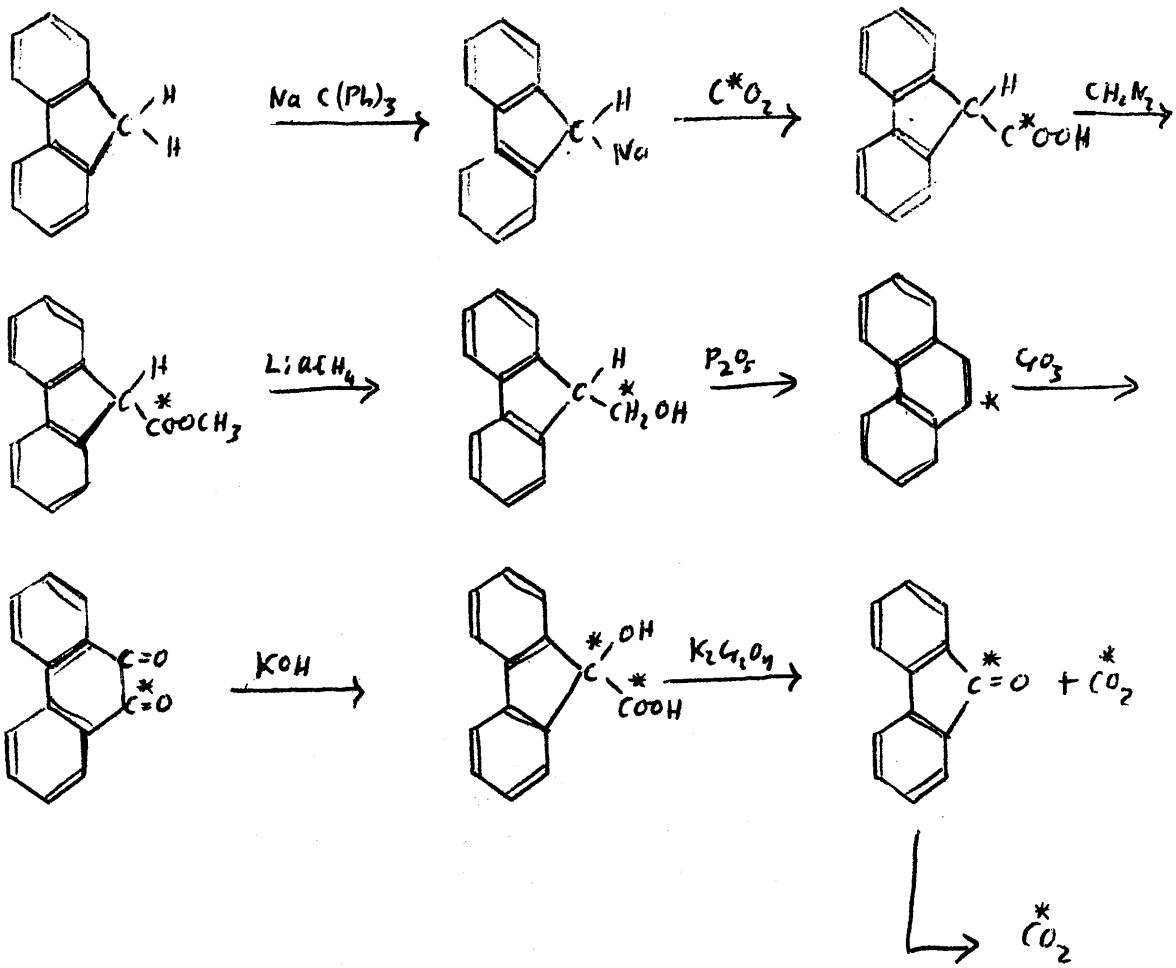
From the results obtained, knowing, from the previous results, the directive effects in the benzilic acid and Wagner re-arrangement, some suggestions as to the electronic distribution in the benz(a)anthracene are made.

Further, from the unsubstituted series any isotope effect involved in the re-arrangement is measurable.

Summary.

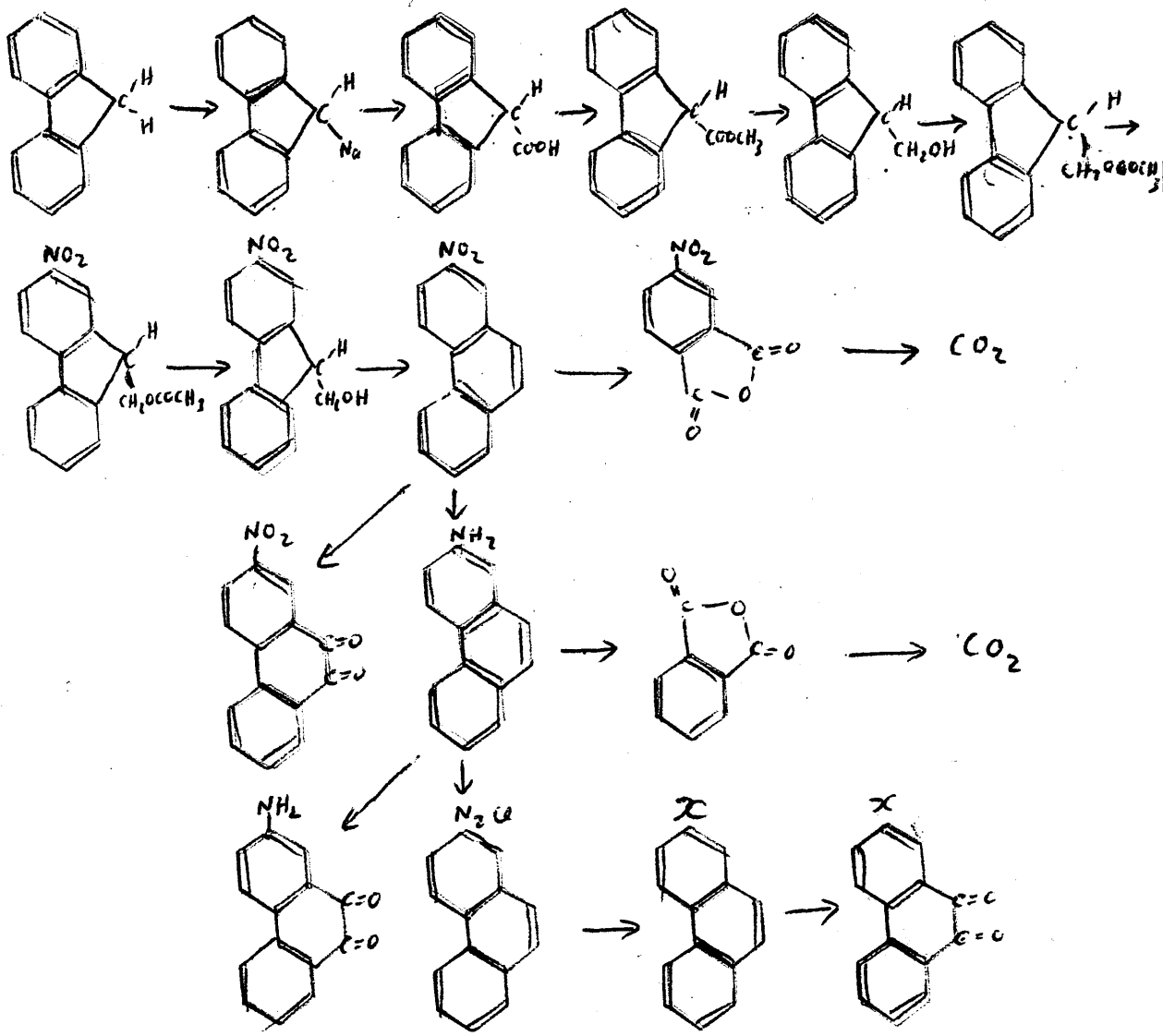
The sequences involved are diagrammatically represented below.

1. The unsubstituted series.

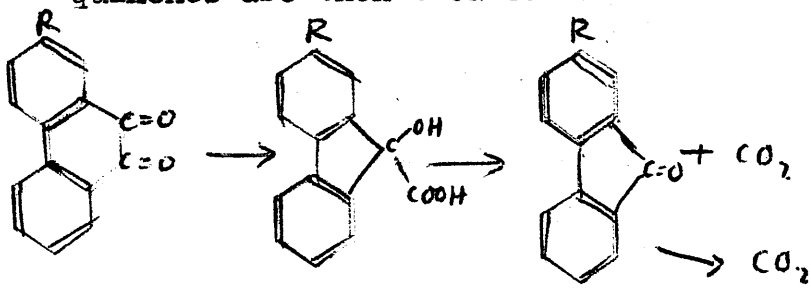


This gives information regarding the isotope effect.

2) 2 - nitrophenanthrene quinone.



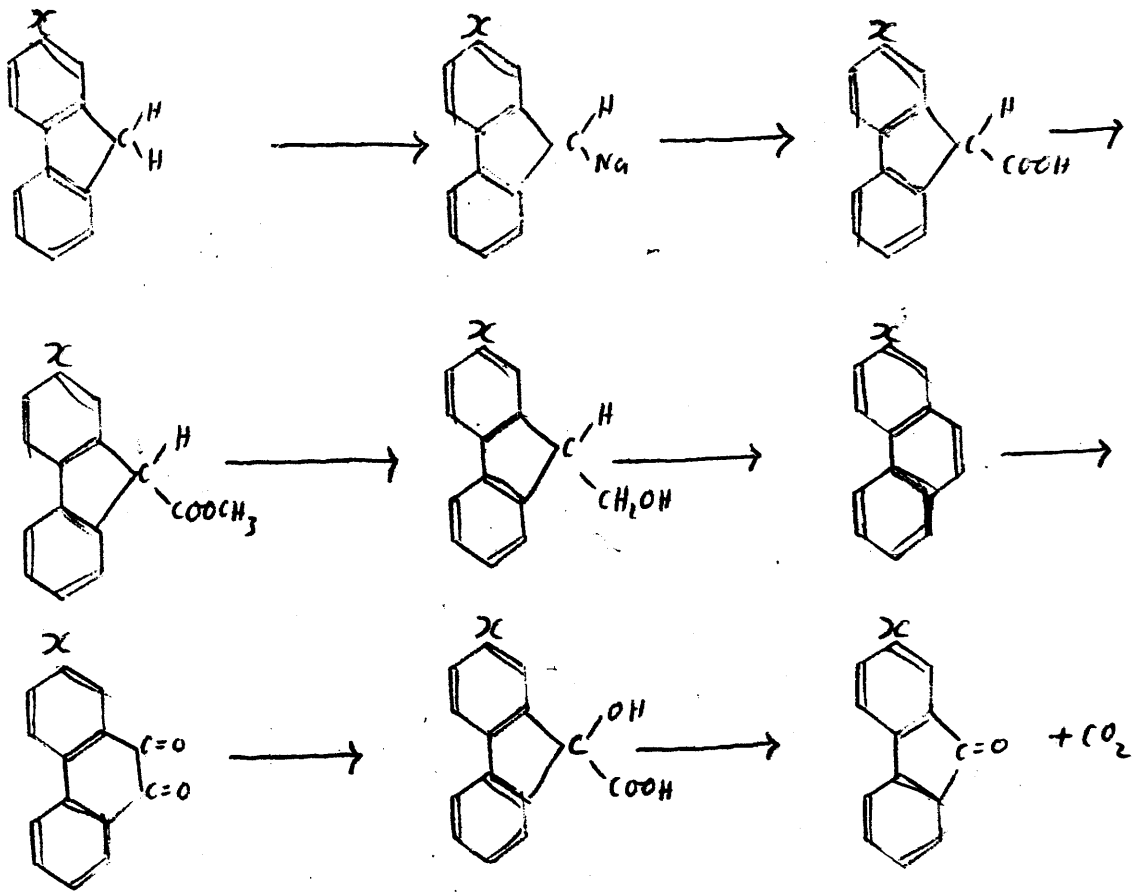
Where X is Cl, Br, I, O-CH_3, OH. The resulting quinones are then treated as before.



Where R is NO_2, NH_2, Cl, Br, I, OH or OCH_3.
This was the synthesis adopted after various attempts to prepare 2-nitrophenanthrene labelled differently at positions 9 and 10.

3) The Wagner Re-arrangement

The Following sequence was employed for the preparation of the various other substituted fluorene-9-carbinols for the survey of the Wagner re-arrangement.



Where X is chloro, bromo, iodo or methoxy.

4) 2 Methyl-, 2 Ethyl fluorene.

This same sequence was also carried out, from substituted fluorene to substituted fluorenone and hence to carbon dioxide, using the 2-methyl and 2-ethyl fluorenes. The results were, however, difficult to interpret, since only the final distribution of the ^{13}C isotope in the alkyl fluorene-hydroxy-carboxylic acids was obtained. The relative distribution of the isotope before the benzilic acid re-arrangement, i.e. at the alkyl phenanthrene-quinone stage, could only be suggested, and hence the redistribution of the isotope, occurring during the benzilic acid re-arrangement, could only be suggested.

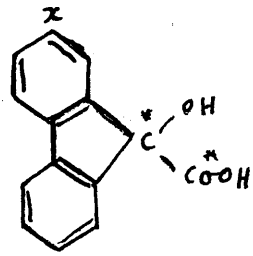
RESULTS.

The assays of the carbon dioxide samples were carried out on a Metropolitan-Vickers M.S.2. Mass Spectrometer. For each sample the relative proportions of material of mass number 44 and of mass number 45 were measured, i.e. $^{12}C^{16}O_2$ and $^{13}C^{16}O_2$. A contribution to the height of the peak at mass number 45 would be made by $^{12}C^{16}O^{17}O$ but, since the natural abundance of the ^{17}O isotope is only 0·04%, this would not be significant.

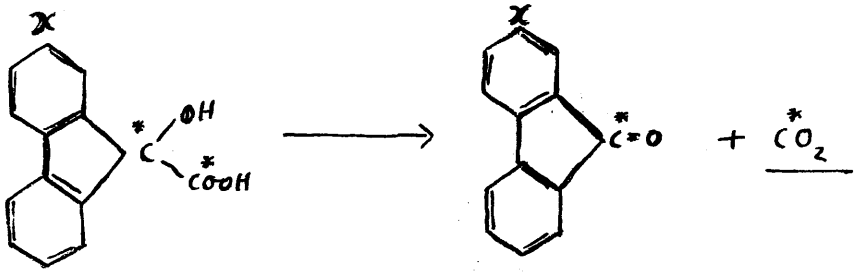
In each case the percentage of ^{13}C is calculated. From this the distribution of ^{13}C, across the relevant positions in the molecules, is calculated.

Three distributions occur:-

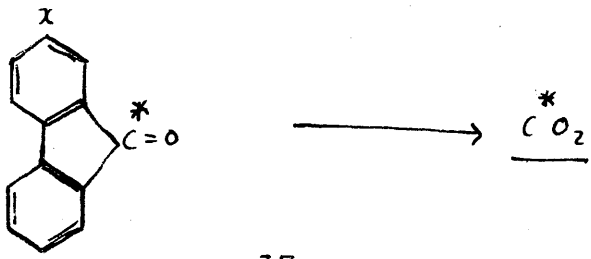
1. Across positions 9 and 10 in the various fluorene-9-carbinols.
2. Across positions 9 and 10 in the various phenanthrenes derived from the carbinols by the Wagner re-arrangement. This is given in the case of the nitro series by the ^{13}C concentration in the nitrophthalic and phthalic anhydrides after combustion to carbon dioxide.
3. Across positions 9 and the carboxylic acid carbon in the various fluorene 9-hydroxy-9-carboxylic acids.



This is given by the carbon dioxide sample obtained on mild oxidation,



and the sample obtained on combustion of the various fluorenones.



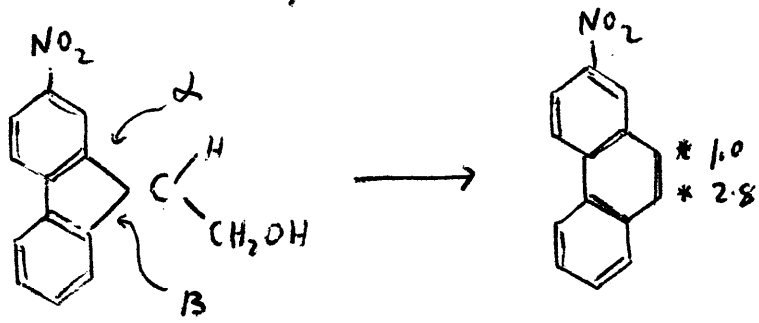
The change in ^{13}C distribution between the carbinol stage and the phenanthrene stage, gives the relative ease of rupture of the two bonds from the benzene rings to C_9. The change in ^{13}C distribution, between the phenanthrenequinone stage and the fluorene-9-hydroxy-9-carboxylic acid, gives the relative ease of rupture of the two bonds connecting C_9 and C_{10}, respectively, with the adjacent carbon of the benzene

rings.

The nitrocarbinol had only position 10, the carbinol carbon, enriched with respect to ^{13}C. If, in the Wagner re-arrangement, both of the bonds from the C_9 position, to the substituted and to the unsubstituted benzene rings respectively, split equally readily, then 50% of the enrichment, originally appearing on the carbinol carbon, would appear at both C_9 and C_{10} in the resulting phenanthrene, when ring enlargement occurred in the carbinol. If one bond ruptured to the complete exclusion of the other, then 100% of the enrichment appearing on the carbinol carbon, would appear at either position 9 or 10 in the resulting nitrophenanthrene. Hence the proportion of ^{13}C enrichment across positions 9 and 10 in the resulting nitrophenanthrene gives the relative ease of splitting of the two bonds during the Wagner re-arrangement.

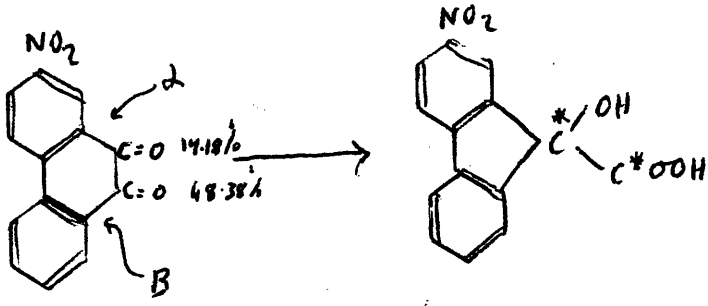
In the case of the nitrofluorene-9-carbinol, for example, originally the carbinol carbon was 65·64% enriched as regards ^{13}C. On effecting the ring enlargement, this enrichment appeared across positions 9 and 10 in the ratio of 2·8 : 1, i.e., if we designate the bond between C_9 and the nitrophenylene ring as α and that between C_9 and the phenylene ring

as β, then β has split more readily than α in the proportion of 2·8 : 1,



The actual amounts of ^{13}C at positions 9 and 10 being 48·38% and 17·18% respectively calculated from the phthalic anhydride samples.

In the fluorene-9-hydroxy-9-carboxylic acids derived from the phenanthrene this proportion will now redistribute itself:-



Should bond α split to the complete exclusion of β then 17·18% ^{13}C will appear at the carboxylic carbon. Should only bond β split then 49·38% ^{13}C will appear at the carboxylic carbon. The relative ease then of migration of the nitrophenylene/ phenylene radicals is given by :-

$$\frac{(X \times 17{\cdot}18) + (1 \times 48{\cdot}38)}{(X+1)} = {}^{13}C \text{ proportion at carboxylic carbon}$$

Where X represents the relative ease of migration of the two radicals.

The ^{13}C proportion at position 9 in the 2-nitro phenanthrenequinone is given by the ^{13}C content for the phthalic anhydride sample derived from this 2-nitrophenanthrenequinone.

The proportion at position 10 may be obtained either from the nitrophthalic anhydride sample or by difference between the enrichment at position 9 and the total ^{13}C enrichment in the complete nitrophenanthrene molecule.

The table of numerical results (page 37) gives thus:-

(1) Percentage ^{13}C at C_9 derived from phthalic anhydride 48·38

(2) Percentage ^{13}C at C_{10} derived from nitrophthalic anhydride 17·18

(3) Percentage ^{13}C at $C_9 + C_{10}$ derived from nitrofluorene carbinol 65·64

(4) Percentage ^{13}C at C_{10} by difference (3) - (1) = 17·26.

The figure obtained in (4) agrees closely with that obtained in (2).

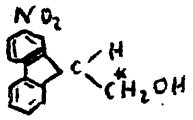
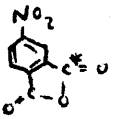
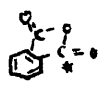
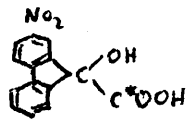
Similarly in the various fluorene hydroxy carboxylic acids the ^{13}C abundance at the carboxylic acid carbon

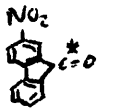
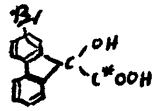
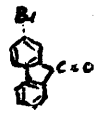
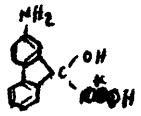
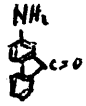
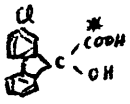
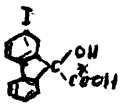
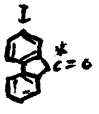
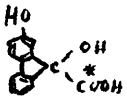
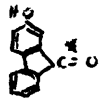
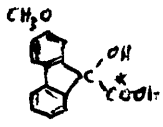
could be obtained by mild oxidation of the acid to the corresponding substituted fluorenone and carbon dioxide, the carbon dioxide being assayed directly for ^{13}C content. The ^{13}C concentration at the C_9 position could then be obtained, either by oxidising the substituted fluorenone to carbon dioxide and assaying the carbon dioxide sample directly, or by difference between the total activity of the hydroxy acid and the activity due to the carboxylic acid carbon.

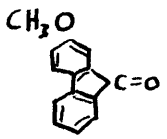
Numerical Results.

The table below gives the ^{13}C abundance ratios obtained from the various carbon dioxide samples submitted to the mass spectrometer. This ratio is obtained directly from a comparison of the peaks at mass weights 44 and 45. The third column in the table gives the abundance ratio expressed as a percentage ^{13}C and the fourth column gives the calculated percentage of ^{13}C at the relevant position in the molecule under consideration. The calculation of a typical example is appended. The abundance ratio is an average of a dozen mass spectrometer readings in each case.

Table 1.

1. CO_2 sample derived from:-	2. $^{13}C/^{12}C$ abundance ratio	3. $^{13}C/^{13}C+^{12}C$ percentage ^{13}C	4. Percentage ^{13}C at relevant position
Ba C^*O_3	2·00	66·67	66·67
	0·0606	5·71	65·64
	0·0321	3·11	17·18
	0·0754	7·01	48·38
	0·242	19.48	19.48

1.	2.	3.	4.
	0·0474	4·53	45·69
	0·309	23·61	23·61
	0·044	4·21	41·53
	0·501	33·38	33·38
	0·0356	3·44	31·52
	0·350	25·92	25·92
	0·042	4·03	39·19
	0·365	26·74	26·74
	0·041	3·94	38·02
	0·745	42·69	42·69
	0·0282	2·74	22·42
	0·468	31·88	31·88

1.	2.	3.	4.
	0·0348	3·36	32·74

The natural ratio of $^{13}C/^{12}C$ is 0·011, so, to calculate column four, allowance must be made for this. If it is assumed that in the case of the 2-methoxy fluorenone, for example, enrichment as regards ^{13}C above the natural figure is all due to enrichment at position 9, the carbonyl carbon, then the abundance ratio $^{13}C/^{12}C$ gives the proportion of ^{13}C: ^{12}C in a molecule in which thirteen of the carbon atoms bear the natural $^{13}C/^{12}C$ ratio of 0·011 and the remaining carbon atom an increased ratio y, where y is given by:-

$$14 \times 3{\cdot}36 = 13 \times 1{\cdot}1 + y$$

whence $y = 32{\cdot}74$ the figure given in column four of the table, expressing the proportion $^{13}C/^{12}C$ as a percentage.

From these results we can calculate the relative ease of migration of the substituted and non-substituted phenylene groups in the course of the benzilic acid re-arrangement.

2-nitrophenanthrene -quinone — percentage ^{13}C at C_{10} = 17·18
percentage ^{13}C at C_9 = 48·38

These figures are derived from the nitrophthalic and phthalic acid anhydrides figures in the table 1. They

give a ratio for ^{13}C between positions C_9 and C_{10} in the 2-nitro-phenanthrenequinone sample, of 2:8:1

Table II

Relative ease of migration of the substituted and non-substituted phenylene groups in 2-R-phenanthrene-quinone.

R.	Percentage ^{13}C at C_9 in resulting hydroxy acid	Percentage ^{13}C at carboxylic acid carbon	X:1
2-nitro	45·69	19·48	12·56
2-bromo	41·53	23·61	3·85
2-chloro	39·19	25·92	2·57
2-iodo	38·02	26·74	2·26
2-methoxy	32·74	31·88	1·12
2-amino	31·52	33·37	0·93
2-hydroxy	22·42	42·69	0·22

where x is the relative ease of migration of the substi-

tuted and non-substituted phenylene groups.

The percentage ^{13}C at the carboxylic acid carbon in the various fluorene hydroxy acids is obtained directly from these acids by liberation of this carbon as carbon dioxide by mild oxidation, and is given in table I. The percentage ^{13}C at position 9 in the various hydroxy acids is obtained by assay of the carbon dioxide obtained on wet combustion of the relevant fluorenone, and is given in table I.

"x" is calculated as follows for a typical case.

e.g. the case of the 2-bromo derivative.

In bromophenanthrene -quinone ^{13}C percent.at C_9= 48·38 ^{13}C percent.at C_{10}=17·18 Derived from phthalic anhydrides figures.

In bromo-fluorene-9-hydroxy 9-carboxylic acid ^{13}C percent.at carboxylic carbon = 23·61

^{13}C percent.at C_9 = 41·53.

The relative ease of splitting of bond α : bond β is:-

$$\frac{(X \times 17{\cdot}18)+(1 \times 48{\cdot}38)}{(X+1)} = 23{\cdot}61$$

$$X = 3{\cdot}85.$$

The relative ease of splitting of bond α : bond β could equally well be calculated from the percentage ^{13}C at C_9, the higher concentration in the

sample derived from the carboxylic acid carbon, however, presumably renders this the more accurate standard.

The Wagner Re-arrangement.

Taking the relative enrichment at the hydroxy acid stage for the 2-nitro, 2-chloro, 2-bromo, 2-iodo and 2-methoxy series as being that given by "x" in table II for these compounds, and carrying out the synthesis on the corresponding fluorene compounds, assay of the resulting substituted fluorenones gives the following results:-

Table III

R	$^{13}C/^{12}C$	% ^{13}C at C_9 in acid	"x" Table II	Calculated % ^{13}C in Phenanthrene C_9	C_{10}	Case of rupture D/B
2-nitro	0·0474	45·6	12·56	47·8	18·2	0·38
2 bromo	0·0383	34·8	3·8	36·1	29·9	0·82
2 chloro	0·0380	34·4	2·57	36·2	29·8	0·82
2 iodo	0·0375	33·7	2·26	34·9	31·1	0·89
2 methoxy	0·0343	32·0	1·12	15·3	56·7	3·31

The columns in table III are calculated as follows, e.g. for the 2-methoxy compound:-

^{13}C abundance ratio = 0·0343

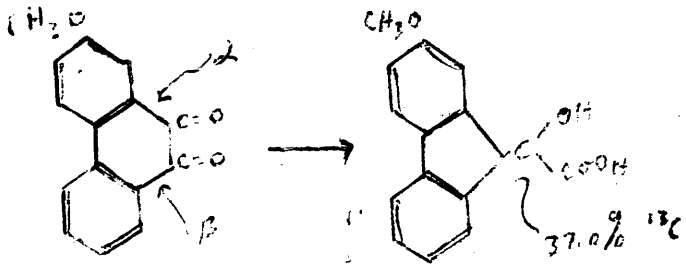
Percentage $^{13}C = \frac{0·0343 \times 100}{1·0343} = 3·31.$

Percentage ^{13}C at relevant position, C_9, is given by

$14 \times 3·31 = 13 \times 1·1 + X$ (1·1 is natural % ^{13}C ratio)

i.e. X = 32·0 where X = percentage ^{13}C at position 9.

Unfortunately we have no accurate figure for the total ^{13}C content of the molecule. The synthesis was begun with $Ba^{13}CO_3$ that was estimated to have a $^{13}C/ (^{13}C+^{12}C)$ ratio of 66·6% and it was assumed that this enrichment would appear at the carbinol carbon in the various fluorene-9-carbinols. However, inspection of the earlier table shows that in the 2-nitro-fluorene 9-carbinol the percentage ^{13}C at the carbinol carbon is only 65·64, and in the final 2-nitro-fluorene-9-hydroxy-9-carboxylic acid the ^{13}C percentage at positions 9 and the carboxylic acid carbon are 45·69 and 19·48 respectively, a total of 65·17. i.e. In the nitro series between the barium carbonate stage, and the carbinol stage, and the final hydroxy acid stage, the ^{13}C enrichment has fallen from 66·6 → 65·64 → 65·17. While this order of error will not effect the qualitative conclusions arrived at, it introduces some doubt into the quantitative results. The nitro series contained three stages more, before the ring enlargement stage, than the other series did. It is therefore perhaps acceptable to suggest that the total ^{13}C enrichment will lie between 66·6% and 65·6%. It has thus been taken arbitrarily at 66·0% in the following calculations with the reservation that this is only an arbitrary figure.



If the ratio of ease of splitting of $\alpha : \beta$ is as given before in table II "x" - i.e. 1·12 for this particular case, then we have:-

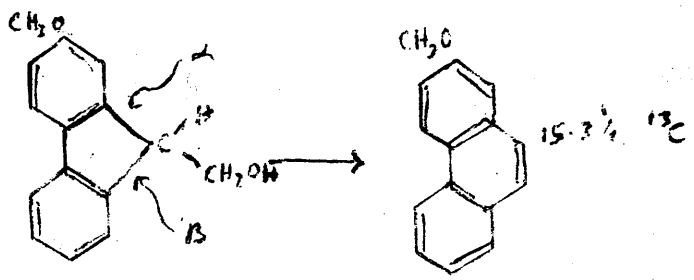
$$\frac{(\text{"X"} \times y) + (1 \times \overline{66{\cdot}0 - y})}{(1 + \text{"X"})} = 32{\cdot}0$$

$$\frac{(1{\cdot}12\ y) + (66{\cdot}0 - y)}{2{\cdot}12} = 32{\cdot}0$$

whence y = 15·3 where "y" is percentage ^{13}C at position 9. in the substituted phenanthrenequinone.

Hence percentage ^{13}C at position 10. is

$$(66{\cdot}0 - 15{\cdot}3) = 50{\cdot}7.$$



Ease of rupture of $\frac{\alpha}{\beta} = \frac{(66{\cdot}0 - 15{\cdot}3)}{15{\cdot}3} = 3.31$

The Isotope Effect.

Table IV

Relative proportion of ^{13}C across the hydroxy acid in the unsubstituted series.

	$^{13}C/^{12}C$	% ^{13}C at carboxylic carbon
Carbon dioxide sample derived from fluorene-9-hydroxy 9 carboxylic acid	0·488	32·80
		% ^{13}C at carbonyl carbon
carbon dioxide sample derived from fluorenone	0·0365	32·56

Total ^{13}C enrichment across C_9 and C_{10} = 65·36

$$\frac{X \times 65{\cdot}36}{1+X} = 32{\cdot}8$$

whence X is not significantly different from unity. i.e. no correction need be applied to the foregoing results to allow for any "isotope effect" involved in the splitting of the ^{13}C–^{12}C compared with the ^{12}C–^{12}C bonds.

The Benzanthracene Series.

Table 5.

	$^{13}C/^{12}C$	$^{13}C\%$ at carbonyl in 1:2 benfluorenone
CO_2 sample derived from 1:2 benzfluorenone	0·021	17·42

The $^{13}C\%$ at the carbonyl carbon in 1:2 benzfluorenone gives the ^{13}C percentage at position 5 in the benzanthracene. i.e. C_5 is 17·42% enriched

C_6 is 48·58% enriched. (66·0 - 17·42).

	$^{13}C/^{12}C$	$\%^{13}C$ at carboxylic carbon
CO_2 sample derived from carboxylic acid.	0·330	24·8

---

^{13}C percentage at C_5 in benzanthraquinone=17·42.

^{13}C percentage at carboxylic carbon =24·80

$$\frac{(X \times 17{\cdot}42)+(1 \times 48{\cdot}58)}{X+1} = 24{\cdot}8$$

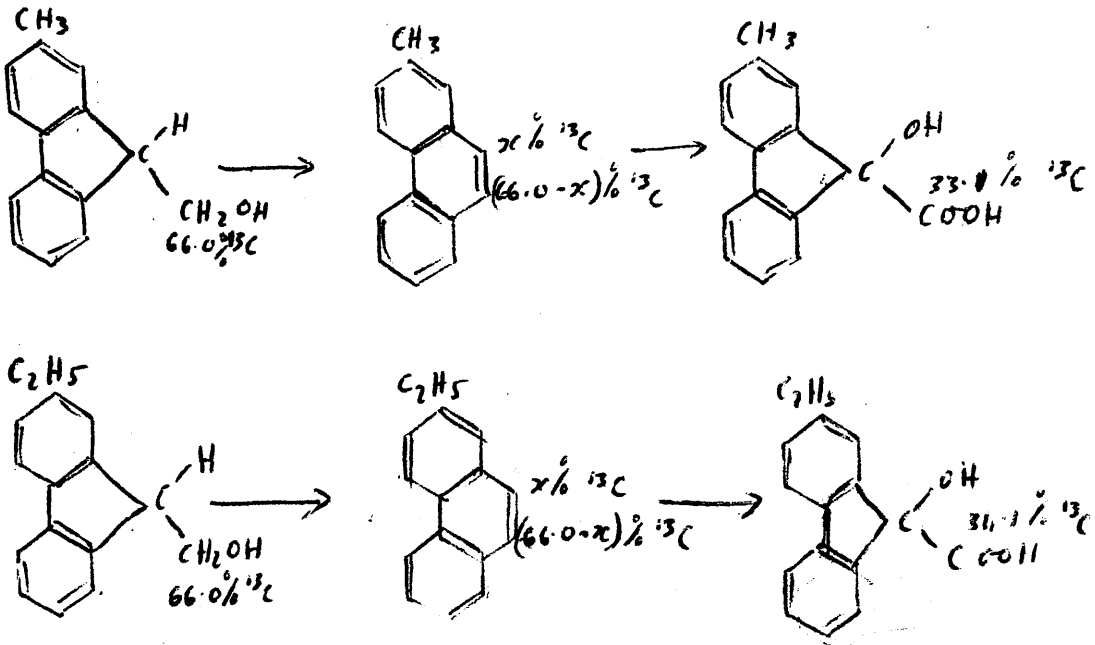
$$X = 3{\cdot}22.$$

---

i.e. the bond from the carbonyl group to the unsubstituted benzene ring split 3·22 times more readily, than the bond from the other carbonyl group to the benz-substituted benzene ring and the proportion of ^{13}C across positions 5 and 6 in the benzanthracene was 1: 2·8

2 Methyl and 2 Ethyl Series.

Substituted fluorenone	$^{13}C/^{12}C$	% ^{13}C at carboxylic carbon of hydroxy acid	% ^{13}C at position 9 in carbinol
2 Methyl	0·034	33·1	66·0
2 Ethyl	0·033	34·1	66·0



The amount of re-arrangement at the two stages cannot be given. Knowing the weak positive inductive effect of the methyl group and ethyl group, it could, perhaps, be suggested by analogy with previous results that, in the substituted phenanthrene, position 9 would be slightly more, and position 10 slightly less, than $\frac{66·0\%}{2}$ enriched.

In the carboxylic acid group of the substituted fluorene hydroxy acid for the methyl and ethyl series respectively 33·1% and 34·1% enrichment appear, i.e., slightly more than 50% of the relative enrichment.

In the previous series the carboxylic acid carbon was less enriched than C_9 where the substituent at position 2 was negatively inductive (Ingold's - I effect) so, by analogy, the carboxylic acid carbon should be more enriched where the substituent is positively inductive.

THEORETICAL DISCUSSION.

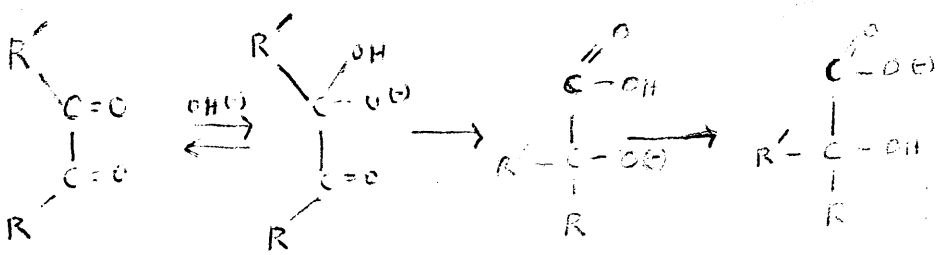
1. Benzilic Acid Re-arrangement.

Previous evidence, see Historical Survey, points to a mechanism involving,

(1) Attack by an hydroxyl ion to form a benzil monohydrate, a fast reversible action.

(2) Slow splitting off of a phenyl group with re-combination at the non-hydrated carbinol carbon which represents a more positive centre than the hydrated carbinol carbon.

(3) Rapid shift of a proton to the more electronegative carbonyl oxygen.



The relative ease of splitting of "α", the bond from the carbonyl carbon, to the substituted benzene ring, and "β" the bond from the carbonyl carbon to the unsubstituted benzene ring is given in the following table. It includes results from other sources, see Historical Survey.

Substituent in substituted ring	Relative ease of rupture of $\alpha : \beta$	System
2-nitro	12·56	phenanthrene-quinone
2-bromo	3·85	
2-chloro	2·57	
2-iodo	2·26	
2-methoxy	1·12	
2.amino	0·93	
2-hydroxy	0·22	
p-methoxy	0·55[38]	benzilic acid
p-chloro	1·56[37]	
2-methyl	< 1	phenanthrene-quinone
2-ethyl	< 1	

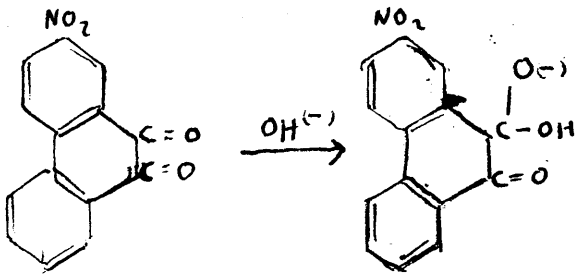
The 2-position substituents are all in the meta position to the carbonyl group. The effect of these groups will be inductive, or the mesomeric effect on the positions adjacent to the carbonyl group may be relayed to the carbonyl group by an inductive mechanism.

The 2-methyl and 2-ethyl series, as mentioned previously, were dealt with differently from the others and no accurate value for the relative ease of rupture of the α and β bonds in the relevant quinones can be given.

2-Nitro substituent.

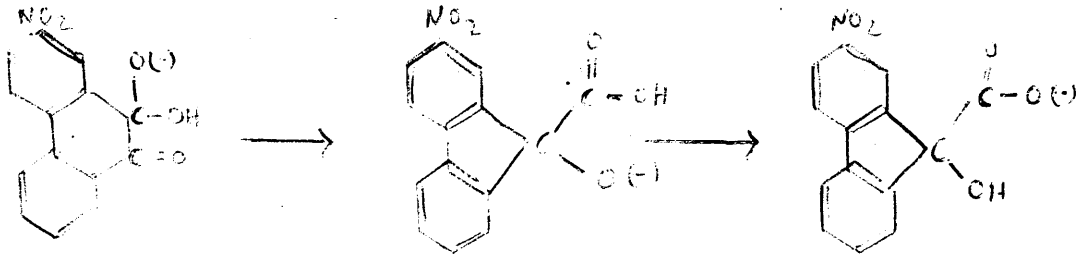
The nitro group relative to hydrogen is strongly negatively inductive, for example, the ionisation

constant for benzoic acid is only $6 \cdot 27 \times 10^{-5}$ whereas for m-nitro benzoic acid it is $32 \cdot 1 \times 10^{-5}$ (Dippy[55]). In the 2-nitrophenanthrenequinone the ring containing the nitro-group will be de-activated to electrophilic attack and the carbonyl carbon atom, C_{10}, adjacent to this ring, will be more electron deficient than the other carbonyl carbon atom, C_9. Hence attack by the nucleophilic hydroxyl ion would be favoured at C_{10} over C_9. From the ion so formed either an hydroxyl or phenyl group can split off:-



Loss of the hydroxyl group would reform the phenanthrenequinone. Loss of the phenyl group would give rise to two possibilities, the group could recombine on its original carbon with expulsion of the hydroxyl ion, or it could combine on the other carbonyl carbon. Once the hydroxyl ion has combined on carbonyl carbon atom 10, C_9 would represent a more negative centre favouring recombination by the phenyl group at this point. A proton shift to the more

electronegative oxygen would then give fluorene-9-hydroxy-9-carboxylate ion.



The relative ease of splitting off of hydroxyl or phenyl would depend on the electropositivity of the carbon atom of the phenyl group attached to C_10. The more electropositive this carbon atom, the weaker would be the bond between it and the carbonyl carbon atom C_{10} with its tendency towards positivity. Any substituent on the ring causing an electron deficiency at the carbon atom attached to the carbonyl carbon C_{10}, would hence favour the rupture of the bond between these two positions.

The nitro group thus favours the reaction

(a) by increasing the electropositivity of carbonyl carbon atom 10 and hence favouring attack by the nucleophilic hydroxyl ion at this point.

(b) by favouring rupture of the bond between carbon atom C_{10} and the phenyl group, after formation of the complex hydroxyl ion, slow re-arrangement of this latter ion gives the fluorene-9-hydroxy-9-carboxylate

ion. The large relative ratio for the rupture of the bonds from the substituted and unsubstituted rings gives a measure of the extent to which the nitro group favours the reaction.

The 2-Halo-substituents.

The relative ease of rupture of the two bonds "α" and "β" is less marked in the case of the halogens. These are less strongly negatively inductive than the nitro group. The inductive effects of the halogens decrease in the order F > Cl > Br > I. However with a halogen substituted aromatic ring there operates an electron repulsive effect, the so called "mesomeric effect" of the halogens, which apparently decreases in the order F > Cl > Br > I. This accounts for the rather similar relative ease of rupture of the "α" and "β" bonds obtained in the cases of the 2-bromo, 2-chloro, and 2-iodo phenanthrenequinones, the 2-bromo group, indeed, being the group with the largest effect of the three, this, no doubt, being due to the mesomeric effect on adjacent carbons being relayed by an inductive mechanism to the carbon atom attached to the carbonyl group. A similar effect is noted in the case of the meta-substituted halogen benzoic acids the strongest of which is the m-bromo acid. The relevant values of the ionisation constants being $15{\cdot}4 \times 10^{-5}$ for the meta-bromo, $14{\cdot}8 \times 10^{-5}$ for meta-chloro, and $14{\cdot}1 \times 10^{-5}$ for

meta-iodobenzoic acid. Similarly the rates of alkaline hydrolysis for the esters of these acids have the values of $39{\cdot}5 \times 10^{-2}$ and $36{\cdot}3 \times 10^{-2}$, for the meta-bromo, and meta-chlorobenzoic acid esters respectively. See Bird and Ingold[56] and Kindler[57].

2-Methoxy.

The methoxy group is strongly positively mesomeric and fairly weakly negatively inductive. In the present case the 2-methoxy group shows a very slight facilitation of the reaction, which would be in keeping with the slight negatively inductive effect of meta-methoxy. e.g., the ionisation constant for benzoic acid is $6{\cdot}27 \times 10^{-5}$ while that for m-methoxy benzoic acid is $8{\cdot}17 \times 10^{-5}$.

2-Amino.

This shows a slight retardation of the reaction. The amino group is weakly negatively inductive and strongly positively mesomeric. Relay of the positive mesomeric effect from adjacent carbons to the meta position would tend to overcome the weak inductive effect. The result obtained for the relative ease of bond rupture, 0·92, seems to indicate that the relayed mesomeric effect is overcoming the inductive effect. Due to Zwitterionic effects

ionisation constants of the corresponding acids are probably not strictly comparable with the present case but K x 10^{-5} benzoic acid = 6·52 and for m-amino benzoic acid is 1·63.

2-Hydroxy.

The hydroxyl group is again weakly negatively inductive and strongly positively mesomeric. However the benzilic acid re-arrangement is conducted in 10% caustic soda solution, under which conditions the hydroxyl group would be present not as OH but as $-O^{(-)}$, which would be strongly electron repelling. In the present case the ease of splitting of the two bonds is 4·55:1 in the favour of the bond remote from the hydroxyl group which must then represent the more positive centre. The relative ease of splitting of the α and β bonds in the 2-hydroxy phenanthrenequinone would depend on the degree to which the hydroxyl group is ionised, which would depend on the p^H of the solution during the re-arrangement.

Methyl and Ethyl.

As remarked before, the results for these groups were difficult to interpret but they would seem to suggest again preferential splitting of the bond attached to the unsubstituted ring which would be in agreement with the known positively inductive effect of these groups.

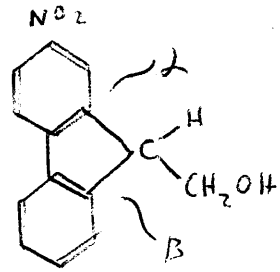
For p-Chlorobenzil, Neville gives the relative ease of migration of the chlorophenyl and phenyl groups as 61:39 or 1·56:1. The figure obtained in the present work for meta-chloro in the slightly different phenanthrenequinone series is 2·5:1. This is in keeping with the known character of the chloro group which is strongly positively mesomeric, with respect to hydrogen. For example, although both meta and para chlorobenzoic acids are stronger than benzoic acid itself, the meta chloro compound is a stronger acid than the para chloro acid. The respective constants are given by Dippy[44] as $14·8 \times 10^{-5}$ and $10·5 \times 10^{-5}$.

The relative ease of migration of the p-methoxy-phenyl and phenyl groups as given by Roberts and Smith - about 1:2 dependant on the temperature of the reaction - would appear to fit into the present scheme, methoxy being fairly strongly positively mesomeric. The figure given by Neville for the same experiment, of 100% migration of the methoxy-phenyl group, seems to be out of keeping with the order of results obtained in the present research.

In the case of groups which have opposite inductive and mesomeric effects, e.g., methoxy, it might be noted that in the substituted phenanthrenequinone although the methoxy group is in the meta position

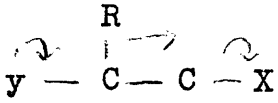
relative to the carbon of the ring attached to carbonyl carbon 10, it is, in effect, at the end of a conjugate system from carbon atom 9. If there is any appreciable conjugation across the whole molecule this will mean enhancement of the relative ease of attack at position 10 over 9. Where the inductive and mesomeric effects are the same, as in the nitro group, it will lower the relative ease of attack at position 10. The relatively low figure for X for the 2-amino quinone considering the relatively weak negatively inductive effect of the group compared with its powerful positive mesomeric effect would suggest that any relaying across the molecule is small.

2. The Wagner Re-arrangement.



In the case of the 2 - nitro fluorene - 9 - carbinol the β link ruptured more readily than the α link. This would imply a preference for a more electronegative centre and hence attack by positive

agent. The re-arrangement is effected by the acid dehydrating agent phosphorous pentoxide. Ingold in his recent book[91] gives as a general scheme for the electronic transfers involved in all saturated nucleophilic re-arrangements:-



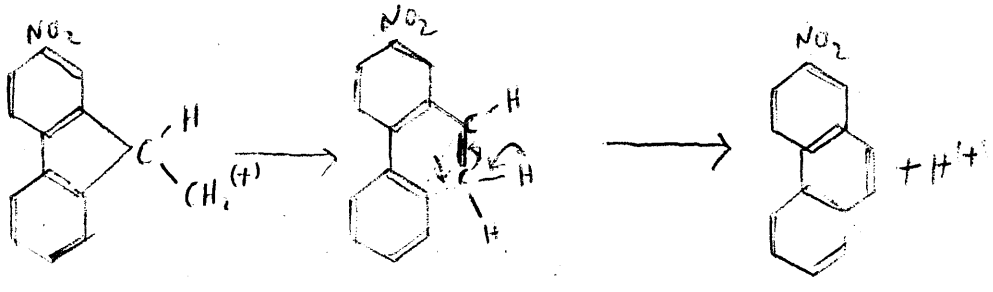
and remarks that "structural changes which should increase the electron supply to the point from which the anion is required facilitate re-arrangement."

Application of the present case to the general scheme gives:-

a) an hydroxyl ion is abstracted from the carbinol by the phosphorous pentoxide

$$P_2O_5 + OH^{(-)} \longrightarrow P_2O_5 \cdot OH^{(-)}$$

b) the resulting positive ion re-arranges, followed by loss of a proton



c) $H^{+} + P_2O_5 \cdot OH^{(-)} \longrightarrow P_2O_5 \cdot H_2O \qquad (HPO_3)_2$

Hence electropositive groups would favour the reaction and electronegative groups retard the reaction. In the cases of 2-nitro, chloro, bromo, and iodo

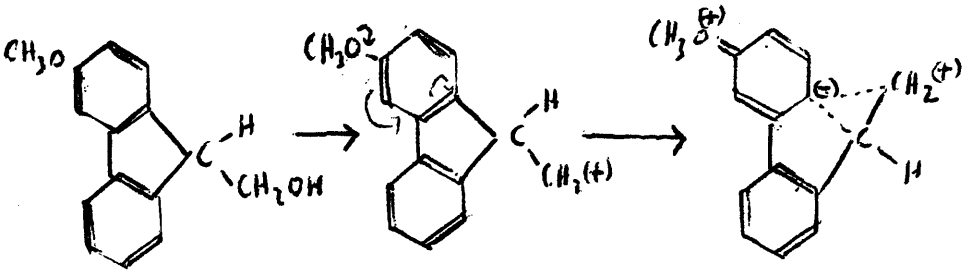
fluorene-9-carbinols the ease of rupture of the α link is lowered, the effect being greatest in the case of the nitro group. The effects of the halogens are again rather similar.

Since the thesis was first compiled, a series of interesting papers on the Wagner re-arrangement have been produced by Collins et al.[58-60] Collins carried out the Wagner re-arrangement of substituted fluorene-9-carbinol, labelled at the carbinol carbon with ^{14}C, and obtained the following results:-

Substituent	% migration of benzo group bearing substituent.	
1 - Methyl	50%	
2-3 - Benz	52%	already quoted
3 - Methyl	73%	
1-2 - Benz	76%	
3 - Methoxy	98%	

In the cases of the 3 methyl and 3 methoxy groups, these are para to the position where bond rupture will occur, and the strongly mesomeric effects of these two groups, are instanced by the very considerable activation of the substituted benzene ring obtained by Collins. The very marked effect of the 3-methoxy group, in particular, must be ascribed to a very pronounced electromeric effect at the demand of the positive charge remaining on

the carbinol carbon after the initial ionisation.

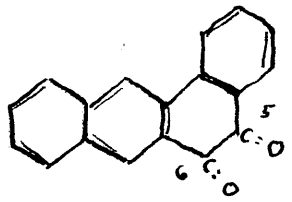


Considerable reversion to the quinonoid form at the demand of the electrophilic group would appear to be occurring.

The 2-methoxy group, from the present research, slightly facilitated the reaction. The normal weakly negative inductive effect of the m-methoxy group, shown, for example, in the results for the benzilic acid re-arrangement, is presumably being overcome by the inductive relaying of the partial negative charges, produced on the adjacent carbon atoms by the very powerful electromeric effect of this group.

Benzanthracene Series.

In the benzanthracene series effected by Collins the ratio ^{14}C at positions 5 and 6 in the benzanthracene was given as 48:52 or 1:1·08. Similarly the ease of rupture of the bonds to these two positions when the quinone was submitted to the benzilic acid re-arrangement was in the ratio of 3·22:1. By analogy with previous results this would suggest that in the compound:-



of the two carbons attached to the carbonyl groups at positions 5 and 6, that attached to position 6 is the more electronegative.

In the Wagner re-arrangement the effect of the various groups was in no case so marked as in the benzilic acid re-arrangement, the latter was, of course, conducted at a lower temperature and hence directive effects in this would be more marked. The higher kinetic energies involved at the higher temperature would make the directive effects of the groups less significant.

This same pronounced effect, of the nitro group in particular, during a reaction involving attack by a negative agent has been noted in the alkaline hydrolysis of substituted benzoic esters e.g.,

comparison of the effects of m-nitro m-chloro, and m-bromo substituents on alkaline hydrolysis of the benzoic esters with the dissociation constants of the corresponding acids gives:-

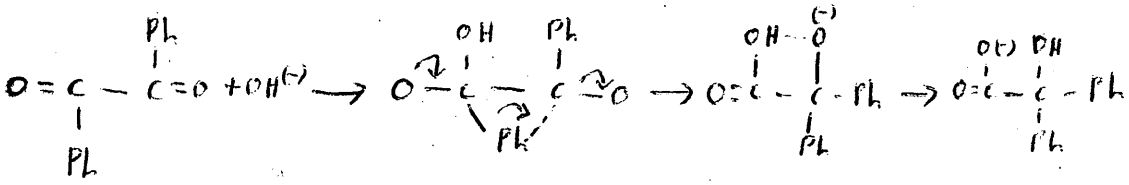
Group X	10^2K for alkaline hydrolysis of X $C_6H_4COOC_2H_5$	10^5K dissociation constants for XC_6H_4COOH
m-nitro	311·0	32·1
m-chloro	36·3	16·8
m.bromo	39·5	15·4
H	4·9	6·27

These figures are due to Kindler and Dippy.

In the alkaline hydrolysis, the introduction of the m-nitro group increases the rate some 60-65 times while it only increases the ionisation of the acid some 5 times compared to the corresponding unsubstituted ester or acid. This is presumably an inductometric effect, produced by the attacking negative ion.

CONCLUSION.

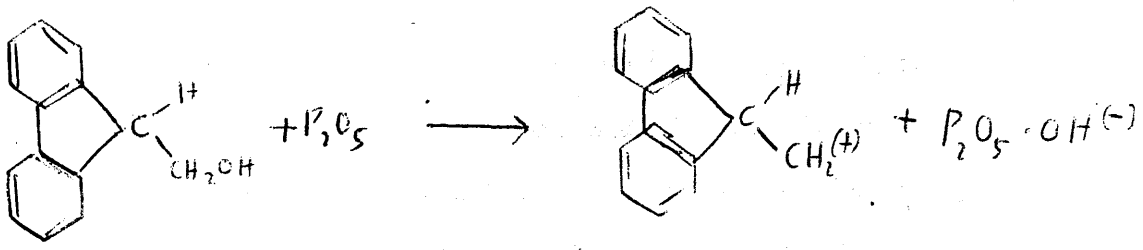
I. The benzilic acid re-arrangement involves attack by hydroxyl ion on benzil. The resulting ion then re-arranges to give benzilic acid. The change is facilitated by electronegative groups and is formulated

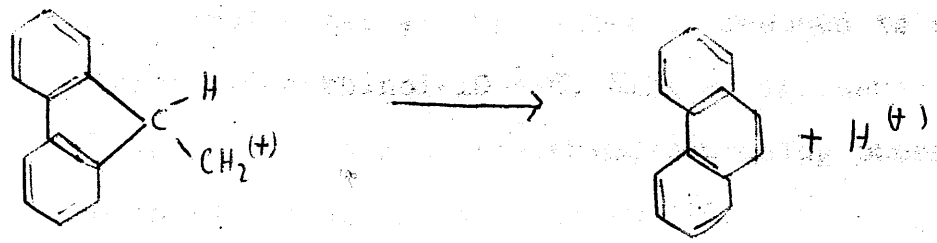


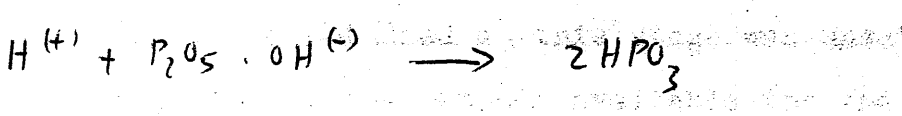
The results of the present isotopic investigations of the effect of the various groups on the benzilic acid re-arrangement, are in complete agreement with this scheme.

II. The Wagner re-arrangement involved in the ring enlargement of fluorene-9-carbinol to phenanthrene by the action of phosphorous pentoxide takes place by ionisation of the carbinol with loss of $OH^{(-)}$ to the phosphorous pentoxide followed by re-arrangement of the positive ion so formed and loss of a hydrogen proton. The reaction is effected in the presence of acid dehydrating agents and is

facilitated by electropositive groups.







EXPERIMENTAL.

1. Unsubstituted Series.

Phenanthrene-9-^{13}C was prepared by a method which was essentially that due to Collins[52]. Fluorene is converted to sodio-fluorene which is then carboxylated with $^{13}CO_2$ to give fluorene-9-carboxylic acid-10-^{13}C. This is esterified to give the methyl ester and the ester is reduced to give fluorene-9-carbinol-10-^{13}C. Ring enlargement of this by means of a Wagner re-arrangementusing phosphorous pentoxide gives phenanthrene-9-^{13}C.

Fluorene-9-Carboxylic acid-10-^{13}C.

The yield obtained at this stage was unsatisfactory and a review of the methods available for the carboxylation of fluorene was made. These included:-

a) via sodiofluorene, prepared by the action of sodio-triphenyl-methyl on fluorene. (Burtner and Cusic[61])

b) via lithiofluorene, prepared by the action of butyl-lithium on fluorene (Schlenk and Bergman[62])

c) via potassiofluorene, prepared by the action of potassamide on fluorene (Yost and Hauser[63]).

d) via sodiofluorene, prepared by the action of sodamide on fluorene (Greenhow, White, McNeill[64]).

(e) via 9-fluorenyl magnesium bromide by a standard Grignard reaction (Miller and Bachmann[65]).

Of these methods c) and d) gave excellant results on the large scale.

Potassium (21·5gm) was dissolved in 800 c.c. liquid ammonia contained in a large flask fitted with a solid-CO_2 condenser, fluorene (84gm) dissolved in ether (800 c.c.) was added and the whole heated on the water bath, the solid-CO_2 condenser being replaced by a normal Liebig condenser. As the ammonia escaped, the level was maintained by making the volume up with ether. A solid orange/brown suspension was obtained of the potassio-fluorene which was treated with solid powdered carbon dioxide (400gm) to yield fluorene-9-carboxylic acid (94·5gm) in 90% yield.

Fluorene (183gm), sodamide (39gm) and decahydronaphthalene (400 c.c.) were boiled together for four hours to give a brownish/yellow solid, sodiofluorene, which was filtered, washed quickly with ether, suspended in ether, and treated with excess dry powdered solid carbon dioxide to give fluorene-9-carboxylic acid (190gm = 81% of theory).

However, neither of these methods was suitable on a 100mg. scale, the manipulation of the small amounts of potassium and liquid ammonia involved in the former, and the difficulty in getting reproducible results in the latter process, caused these methods

to be abandoned. As regards the latter process, six different runs were attempted using 183mg., of fluorene, 39mg.. of sodamide and 5cc of decahydronaphthalene refluxed in an evacuated system using an external condenser. The product was then frozen and the carbon dioxide liberated from barium carbonate (100mg.) was distilled in, yields of fluorene 9-carboxylic acid ranging from 50 - 85mg., (about 50% - 80%) were obtained. The results were not reproducible, this was considered to be due to variations in the quality of the sodamide used, — for such a small amount, (39mg.), random irregularities in the rather coarse sodamide available would be very significant. Moreover the sodio-fluorene obtained by this method was apparently much less active than that obtained by the sodio-triphenylmethyl method (a) and absorbed carbon dioxide much more slowly. The very important need to have reproducible results, particularly when using isotopic carbon dioxide, caused this method, too, to be abandoned, although it was used for preparing fluorene 9-carboxylic acid on the gramme scale for investigation of the later stages of the synthesis.

Methods b) and c) were slow and gave consistent but rather low yields both on the gramme and milli-

gramme scales. The metallo drivatives were slow and tedious to prepare and reacted slowly and incompletely with carbon dioxide. The difficulty of keeping the active metallo derivative uncontaminated during the long refluxing required, and the low yields obtained, made these methods unattractive.

The sodiotriphenylmethyl method was adopted. The preparation of the sodio metallo derivative of fluorene was also rather slow by the method of Bachmann and Wiselogle[66], about two hours being required to complete the reaction, which involved violently shaking together triphenylmethyl chloride, sodium metal and broken glass in benzene/ether for two hours. However, it was discovered that if the sodium was efficiently stripped of any protective layer of sodium chloride formed during the course of the reaction, the reaction proceeded rapidly to completion. This stripping was effected by smearing the sodium against the walls of a heavy glass reaction tube by a glass stirring rod, equipped with an elliptical glass button at the end, which just fitted the reaction tube, the stirrer being driven by a high speed motor. Under these conditions the reaction went smoothly to completion in about two minutes. The sodio-triphenylmethyl so obtained was frozen in liquid air and a slight excess of fluorene was added to it, the whole

reaction being conducted under nitrogen. This was effected by equipping the reaction tube with a standard B 19 socket, the stirrer fitted through an adapter equipped with inlet and outlet tubes for nitrogen. When the sodio-triphenylmethyl was formed, the stirrer was lifted clear of the reaction mixture, and the latter was frozen in liquid air. Fluorene was added to the solid product and the tube was connected to a standard high vacuum manifold system, and evacuated to a pressure of less than 1.m.m. Hg. The tube was then isolated and allowed to warm up. The sodiotriphenyl-methyl reacted rapidly with the fluorene to give an orange product which was again frozen in liquid air. Carbon dioxide was then distilled into the vessel, which was again isolated and allowed to warm up. The carbon dioxide was rapidly absorbed, as shown by a manometer reading, and when the latter was steady, a little water was added to the vessel to destroy excess sodio-fluorene and sodium.

In a typical run, the sodiotriphenylmethyl obtained from triphenylmethyl chloride (220 mgm.), sodium (80 mgm), and dry ether (3·5 ml.), was treated with fluorene (166 mgm. - 1 m.mole). The carbon dioxide obtained from barium carbonate (100 mgm.) was then distilled in.

The yield of acid based on barium carbonate was consistently between 65–70%. With excess carbon dioxide –as solid carbon dioxide– a consistent yield of about 80% was obtained by this method.

Methyl fluorene 9-carboxylate.

Methylation of the fluorene-9-carboxylic acid by the method of Collins did not give satisfactory results, and various methods of methylating the acid were investigated.

Collins' method consisted of a Freudenberg and Jakob[67] esterification at room temperature, using acetyl chloride as calalyst. In a typical run, Collins took fluorene-carboxylic acid (115·5 mg.) and added a chilled mixture of methanol (5 c.c.) and acetyl chloride (0·1 c.c.). After standing at room temperature for one hour, the mixture was taken to dryness to yield the required ester m.pt. 63·0 – 63·5 in 98% yield. This could not be repeated. Under the above conditions with rigorously dried reactants, a non-solidifying residue was obtained repeatedly, which on extraction with bicarbonate solution, gave an appreciable quantity of unchanged acid, and a still impure ester.

Esterification by the normal methanol process with sulphuric acid was not satisfactory. A yield of ester was

obtained which was partly sulphonated. Using the Fischer Speier method a yield of 90% of substantially pure ester was obtained. However in the subsequent course of the research it became necessary to esterify various substituted fluorene-carboxylic acids and some of these, in particular the 2-nitro fluorene carboxylic acid, decarboxylated completely under the conditions for the Fischer Speier esterification and gave 2-nitrofluorene quantitatively as the sole product. It was important to have consistency throughout the series of experiments and for this reason the milder esterification procedures were investigated.

The silver salt method failed entirely to give any ester product, the silver salt of the acid being recovered unchanged on removing the methyl iodide.

The acid chloride method was sucessful. In a typical run fluorene carboxylic acid was refluxed gently with excess thionyl chloride (100 mg acid in thionyl chloride 2 c.c.) the excess thionyl chloride was removed and methanol (2 c.c.) was added, the product was warmed gently for a few minutes and gave a 95% yield of pure ester on evaporating off the excess solvent.

To complete the survey the Newman[68] method and diazomethane were employed.

In the Newman method the acid (100 mg.) was dissolved in ice-cold concentrated sulphuric acid (2 c.c.) and excess methanol (10 c.c.) added, with stirring. The product was dark coloured and completely water soluble and apparently contained sulphonate groups. It is appreciated that the Newman method is only applicable to those acids which readily yield a positive acyl ion in sulphuric acid.

In conclusion, diazomethane was used as a methylating agent. An ethereal solution of diazomethane was prepared by the usual method from isonitrosomethyl-urea: the solution, dried over caustic soda pellets, was added in excess to the fluorene carboxylic acid (100 mg.). On removing excess ether, the methyl ester was obtained, in quantitative yield, as a pale-yellow, hard, waxy solid melting at 63·5°. Diazomethane was adopted as the standard methylating agent throughout the series.

Fluorene - 9 - carbinol.

The methyl ester was reduced by lithium aluminium hydride. The hydride was crushed and refluxed in dry ether for half an hour; the resulting slurry was added in excess to the fluorene - 9 - carboxylic acid methyl ester (100 mg.). The product, after reaction had subsided, was refluxed gently for half an hour. Moist ether was added, followed by a few drops of water and finally sufficient

dilute hydrochloric acid to give a clear solution. The ether layer was separated, washed and taken to dryness.

The subsequent purification of the carbinol was as described by Collins. The crude carbinol was dissolved in benzene and placed on top of an alumina column. The column was eluted with benzene, the first few millilitres of eluate contained an impure unreduced ester which was discarded. The column was then washed through with alcohol. On taking the first 10 c.c. of alcohol eluate to dryness, the carbinol was obtained as a pure-white solid.
Yield 75 - 80 mgm., of a product melting at 96°.

Phenanthrene.

The carbinol obtained was dehydrated by the method of Brown and Bluestein[69,70]. In a typical run the carbinol (100 mgm) was refluxed with xylene (10 c.c.) - which had previously been refluxed over phosphorous pentoxide and decanted therefrom- with phosphorous pentoxide (1 gm.) for half an hour. The product was decanted free from phosphorous pentoxide and the residue was washed with benzene by decantation. The combined supernatant liquors were evaporated down to small bulk and placed on top of a short alumina/activated carbon (50:50) column. The first few millilitres

of eluate on eluting with benzene gave a product melting at 98° and which was substantially pure phenanthrene. The yield was about 80 mgm., or about 90% of the theoretical.

Phenanthrenequinone.

Phenanthrene (100 mgm.) was dissolved in glacial acetic acid (1 c.c.) at 100° and excess of a saturated solution of chromium trioxide in glacial acetic acid was added to it, dropwise. After the reaction had subsided the product was allowed to stand for one hour in an air oven at 50°. Excess acetic acid was removed by a fine jet of warm air, and water (10 c.c.) added to the residue. The phenanthrenequinone was collected on the pad of a filter stick by reversed filtration. On washing with water and drying, the quinone was obtained pure, in almost quantitative yield. From 100 mgm., of the phenanthrene 100-105 mgm., of the quinone (m.pt. 205°) were obtained.

Fluorene-9-carboxylic acid.

In an actual synthesis the quinone was not isolated, but the pad of wet quinone supported on the filter stick was used as stirrer and the whole inserted in a test tube. Dilute caustic soda, 10% (5 c.c.) was added, stirring commenced, and the whole warmed to 80° in a hot water bath for four hours, by which time complete

solution had occurred. An atmosphere of nitrogen was maintained above the reaction liquid, to prevent air oxidation to fluorenone. The solution was then sucked off through the filter stick with water for washing. Excess dilute hydrochloric acid was added to the filtrate, and the precipitated acid extracted with ether, to give an almost quantitative yield of a product m.pt. 124°. (Literature 125° for the hydrated acid)

Fluorenone.

Several oxidising conditions were tried in the hope of finding an oxidising agent which would oxidise fluorene-9-hydroxy-9-carboxylic to fluorenone, in the cold, quantitatively, - however without success. Finally a dilute solution of potassium dichromate in sulphuric acid was used. The hydroxy acid was heated at 60° for thirty minutes with an excess of the reagent. On extracting the solution with ether, washing the ether extract with water, and taking to dryness, a pale greenish/yellow solid was obtained. This was dissolved in benzene and purified by chromatography on a short alumina column in benzene. The pale yellow band of fluorenone was collected. The product after drying, melted at 82 - 83° (lit. 83·0° - 83·5°). Without isolating at the phenanthrenequinone and fluorene 9-hydroxy-9- carboxylic acid stages, a yield of 65 mgm. of fluorenone of high purity was obtained from phenanthrene (100 mgm.), an

overall yield of 65% or 85% per stage.

In an actual run on isotopic materials the oxidation of the fluorene 9-hydroxy -9carboxylic acid was carried out in a tube attached to a manifold system. The tube was evacuated, the reagent was added, and the tube heated to 60° cautiously for 30 minutes. The product was frozen in solid carbon dioxide, and the carbon dioxide liberated from the hydroxy acid distilled into a phosphorous pentoxide tube cooled in liquid air, the manifold system was evacuated again, isolated and the dried carbon dioxide sample distilled into a standard break-seal tube which was then sealed off, and retained for mass spectrometer assay.

The fluorenone was finally oxidised by the wet combustion method of Van Slyke, Folch and Pliazin[71] to carbon dioxide in a manifold system. The carbon dioxide was dried over phosphorous pentoxide and distilled into a break seal tube as before.

Isotopic synthesis from barium carbonate

The total synthesis

was carried out on 100 mgm. of $BaCO_3$ - 66·6% ^{13}C, the final weighed product was fluorenone of excellant purity, yield about 30 mgm., representing an overall yield of 30% or a yield per stage of over 80% without allowing for inevitable transfer losses. The process for the synthesis was as follows:-

The sodio fluorene obtained, as described elsewhere, from 166 mgm. of fluorene, was frozen in liquid air, and the reaction tube attached to a vacuum manifold and evacuated. The carbon dioxide liberated from barium carbonate - ^{13}C by concentrated sulphuric acid was then distilled, first into a tube containing phosphorous pentoxide and then into the tube containing sodiofluorene which was then isolated and allowed to warm up with stirring. After the reaction, the reaction tube was again frozen, this time in an acetone/solid carbon dioxide bath, and unreacted carbon dioxide distilled back into the phosphorous pentoxide tube for use in the next series. The excess sodium and sodio fluorene was destroyed, the mixture acidified, extracted with ether and the ether extract taken to dryness. Excess diazomethane dissolved in ether was added and the product taken to dryness. A slurry of the lithium aluminium hydride reagent was added in excess, the product was treated with water and hydrochloric acid, and extracted with ether. The ether extract was taken to

dryness, dissolved in benzene (1 c.c.), and placed on top of an alumina column which was eluted with benzene. The column was then washed through with alcohol and the alcohol eluate taken to dryness in a reaction tube. Xylene (5 c.c.) and phosphorous pentoxide (0·5 gms.) were added and the mixture refluxed for 30 minutes. The product was decanted and chromatographed through a short column of alumina/activated charcoal (50:50) in benzene, the eluting benzene being used to wash the residue of phosphorous pentoxide. The eluate was collected directly into a reaction tube. After the first ten millilitres of eluate had collected, the tube was removed, and the eluent was evaporated off in a stream of warm air, leaving a white crystalline residue. Sufficient hot acetic acid was added to dissolve the residue and an excess of chromium trioxide in glacial acetic acidwas added dropwise. After the reaction, the tube was warmed in an air oven for thirty minutes at 50°. Water was added, and the filtrate sucked off through a filter stick until no more chromium was present. Dilute caustic (10% - 10 c.c.) was added and the alkali stirred with a filter stick bearing its pad of quinone, at 80° for four hours. The solution was sucked off through the filter stick and acidified and extracted with ether. The ether extract was taken to dryness in the bottom of a reaction tube which was/

then attached to the manifold system. A solution of potassium dichromate in dilute sulphuric acid was added to the tube after it had been evacuated and isolated. The reaction tube was then warmed to 60° for thirty minutes and then frozen in solid carbon dioxide/acetone. The carbon dioxide in the reaction tube was distilled via a phosphorous pentoxide drying tube to the break-seal sample tube. The residue was extracted with ether and the ether extract taken to dryness. The residual fluorenone was dissolved in benzene and chromatographed through a short alumina column, the yellow band of fluorenone was collected in a reaction tube and oxidised by the Van Slyke reagent, the carbon dioxide sample being collected as before.

This was the standard procedure which was adhered to as strictly as possible for all the subsequent syntheses although departures, particularly in the case of the nitro series, had to be made.

All the intermediates in the above synthesis were prepared on a gramme scale before proceeding with the synthesis on a micro scale. The fluorene was purchased, and purified by chromatography as also was the phenanthrene, the remainder was obtained as follows:-

Fluorene - carboxylic acid.

This was obtained partly by the method of Greenhow, White and McNeil, referred to previously, and partly by the method of Arnold, Parham and Dobson[72] — an excellant method, involving the dehydration of benzilic acid by aluminium trichloride, and yielding pure fluorene - 9 - carboxylic acid in better than 80% yield.

Methyl ester

This was obtained, as described previously, by a standard Fischer Speier esterification from the acid.

Fluorene 9 - carbinol.

This was obtained by the formalin reduction of 9-formyl fluorene according to the method of Brown and Bluestein[70]. Potassium (4·7 gms) was treated with methanol (20 c.c.) which had been rigorously dried. After solution occurred, excess methanol was removed, by heating to 200°, under an atmosphere of nitrogen, in an oil bath. To the resulting potassium methoxide, a solution of fluorene (70 gms) and methyl formate (10 gms) in anhydrous ether (100 c.c.) was added dropwise in the cold. A vigorous reaction set in, after its subsidence,

the mixture was extracted with water, the water extract was acidified with dilute sulphuric acid, and the resulting oil was extracted with ether. (Wislicenus and Waldmuller[73]). The ether solution of 9 - formyl fluorene is smoothly reduced by excess aqueous formalin to give fluorene - 9 - carbinol, which is obtained in long white needles m.pt. 101° on crystallising from petroleum ether.

Phenanthrene-quinone and fluorene-9-hydroxy-9-carboxylic acid.

These were obtained on the gramme scale, by the methods used for preparing these compounds on the small scale.

Phenanthraquinone.

Phenanthrene (30 gms.) was dissolved in warm glacial acetic (150 gms.), and chromic acid (80 gms.) dissolved in glacial acetic (250 gms.) was added slowly. When the reaction subsided, excess acetic acid was distilled off, and the residue treated with water, filtered and washed and recrystallised from alcohol. m.pt. 198-200°. Yield quantitative. - (Graebe[74]).

Fluorene-9-hydroxy-9-carboxylic acid.

Phenanthraquinone (30 gms) was treated with excess caustic soda solution (10%) for four hours with vigorous stirring at 80°. The solution was filtered, rendered acid, and the hydroxy acid filtered off. (Beyer and Friedländer[75]).

Fluorenone.

This was prepared from fluorene by the method of Huntress, Hershberg and Cliff[76], by oxidation with sodium dichromate in acetic acid. Fluorene (200 gms.) is treated with sodium dichromate (600 gms.) and acetic acid (1200 c.c.) under reflux for three hours. The reaction mixture is diluted, filtered, and the residue washed free of chromium salts. The resulting yellow powder is vacuum distilled and the distillate dissolved in benzene, and the fluorenone precipitated from this by petroleum ether, to yield beautiful crystals m.pt. 83°. Yield 70%

THE NITRO SERIES

2 Nitrophenanthrene.

Various attempts were made to reach 2-nitrophenanthrene, all based on the previous method for reaching phenanthrene. It was originally intended to carboxylate 2-nitrofluorene to give the 2 nitrofluorene-9-carboxylic acid.

2 Nitro fluorene.

Fluorene (60 gms) was dissolved in warm glacial acetic acid (500 c.c.) and treated at 50° with concentrated nitric acid (80 c.c.), with rapid stirring, the temperature was finally allowed to reach 80° and the product cooled. On filtering and recrystallising from glacial acetic acid (200 c.c.) 56 gms., of 2 nitrofluorene (mpt. 157°) was obtained. —(Kuhn)[77]

2 Nitrofluorene-9-carboxylic acid

Sodiotriphenylmethyl was prepared as before. On treating this with a slight excess of 2-nitrofluorene, however, only a transient orange compound was obtained. This immediately threw down a white precipitate, presumably by attack on the nitro-group, and on attempted carboxylation, gave no acidic product. Similar attempts using the sodamide method were made without success.

Since the 2-nitrophenanthrene must be differentiated across the C_9 and C_{10} positions, as regards ^{13}C, the nitro group had to be introduced before the ring-enlargement stage. Of the intermediate compounds involved, only 2-nitrofluorene-9-carboxylic acid was described in the literature. Rose[78] obtained this acid by shaking fluorene-9-carboxylic acid in the cold with chloroform and nitric acid. The acid so obtained was impure, and, difficult to purify and esterify because it decarboxylated readily. Attempts to prepare it by nitration of fluorene-9-carboxylic acid methyl ester followed by hydrolysis were unsuccessful, the final product being 2-nitrofluorene. Esterification of the acid, obtained by Rose's method, by the normal Fischer Speier method likewise gave only 2-nitrofluorene.

However the acid could be esterified by the diazomethane method.

Fluorene-9-carboxylic acid (1 gm.) was suspended in chloroform (10 c.c.) and shaken with concentrated nitric acid (3 c.c.) for fifteen minutes. The product was filtered and dried, it was crystallised by being dissolved in the minimum amount of acetone followed by precipitation with chloroform. — Rose's method of crystallisation from acetone/chloroform seemed to cause appreciable decarboxylation—. The dry solid product was suspended in ether and treated with excess diazomethane in ether. The product was taken to

dryness, dissolved in chloroform, and purified by chromatography through a short alumina column. A deep olive-green band developed which was collected and taken to dryness. The product melted at 138°.

This gave a possible method of reaching 2-nitrophenanthrene. The next step in the synthesis, however, would be reduction by lithium aluminium hydride. This reagent with the nitro fluorene carboxylic ester, gave a bright orange diazo compound. To avoid the extra step of further reducing the diazo-compound to the amino compound, it was considered as expedient to begin the synthesis with 2-amino fluorene.

2-Amino fluorene.

This was prepared by reduction of 2-nitro fluorene prepared, as above, according to the method of Kuhn. 2-Nitrofluorene (30 gms) was made into a thin paste with 78% alcohol (1 litre). A solution of calcium chloride (10 gms) in water (15 c.c.) was added together with zinc dust (300 gms). The mixture was refluxed, with stirring for two hours and filtered. On dilution the 2-amino fluorene was precipitated, it was filtered and recrystallised from alcohol (50% - 500 c.c.). The product melted at 127°.

2 - Amino fluorene - 9 - carboxylic acid.

Excess 2-amino fluorene was added to the sodio-triphenyl methyl reagent. A bright orange precipitate

was obtained which was carboxylated by adding solid carbon dioxide. The resulting aminofluorene - 9 - carboxylic acid was soluble in water, and insoluble in organic reagents and difficult to isolate on a small scale. Careful precipitation by adding acetic acid followed by dilute ammonia gave partial precipitation of an acid melting at 205° (lit. 208°). Normally the acid was not isolated. It could not be esterified by diazomethane, since this reagent would attack the amino group, but the reaction mixture was taken to dryness and the residues refluxed with methanol that had previously been saturated with hydrogen chloride. The product was again taken to dryness, caustic soda added, and the product extracted with benzene. The benzene extract was chromatographed on a short alumina column in benzene as eluate, to yield a product, m.pt. 156°, in the form of small iodine-purple needles.

To eliminate the difficulty of dealing with the soluble amino acid, attempts were made to carboxylate the acetylated amino-fluorene, without success. No acid product was obtained, a transient orange compound which immediately decomposed to a white solid, as in the case of the 2-nitro fluorene, being obtained, - due, no doubt, to preferential attack by the sodio-triphenyl methyl reagent on the carbonyl group of the acetyl.

2 Amino - fluorene - 9 - carbinol

The amino ester, obtained as above, was reduced with lithium aluminium hydride. The product was placed on an alumina column and eluted with benzene, a little unreduced ester was first obtained. On washing the column through with acetone, a pale-yellow crystalline solid was obtained melting at 126°.

2 - Nitrofluorene 9 - carbinol.

The amino carbinol, obtained as above, did not stand up to refluxing with xylene and phosphorous pentoxide, it was largely oxidised to tarry impurities.

The amino group had to be reconverted to the nitro-group. The results obtained were unsatisfactory.

The amine was diazotised by sodium nitrite and sulphuric acid, and the diazonium solution run into a solution of sodium nitrite, in water containing cuprocupric sulphite, according to the procedure of Hantszch and Blagden[79]. Similarly, using the method of Starkey[80], only poor yields were obtained. The amine was dissolved in 50% fluoroboric acid, cooled to 0° C, and a 50% solution of sodium nitrite added. The precipitated diazonium borofluoride was filtered off and washed with fluoroboric acid, alcohol and ether. It was added to a suspension of copper bronze in a 50% solution of sodium nitrite at room temperature.

The precipitated nitro compound was purified by chromatography. See Starkey[81]. The yields again were poor and the solid borofluoride difficult to manipulate in small amounts.

It remained to introduce the nitro group after the reduction stage and before the ring enlargement stage i.e. at the carbinol stage. The carbinol itself was largely oxidised on attempted nitration and the alcohol group was protected by acetylation. Fluorene -9-carbinol was treated with ice-cold acetyl chloride, in excess, and the product taken to dryness, dissolved in benzene, and purified by chromatography on an alumina column. The first few cubic centimetres of eluate, on taking to dryness, gave large pale-yellow crystals, melting at 88°, in quantitative yield.

(Found: C, 80·6; H, 5·7; $C_{16}H_{14}O_2$ requires C, 80·5; H, 5·8)

Various methods of nitration were investigated, but were unsuitable, mainly due to oxidative reactions. Eventually, nitration in acetic anhydride at 0° C was decided upon, as the most convenient for small amounts.

The fluorene - 9 - carbinol acetate (100 mgm.), obtained as above, was dissolved in acetic anhydride (1 c.c.) and cooled to 0° C. It was then treated with a mixture of concentrated nitric acid (0·03 c.c.) and acetic anhydride (1 c.c.) and acetic acid (1 c.c.), the acid having been added slowly to the cold mixture of

the other two. The addition of the acid mixture was conducted at such a rate, that the reaction temperature remained below 0° C. The product was well stirred for 1 hour, water was added, and the mixture extracted with benzene. The product was pale-yellow and crystalline and soluble in the normal organic salts and melted at 100 - 120°.

On chromatography through an alumina column, the eluate as it emerged, threw down a white powder which was insoluble in the usual solvents and which burned without melting. This trouble was experienced on attempting to hydrolyse the nitro acetate with dilute sodium hydroxide, and it was assumed to be some sort of base-catalysed condensation. However, on substituting a silica gel chromatograph the nitro acetate could be readily purified. It was obtained as a pale-yellow crystalline solid, melting at 120°. (Found: C, 68·2; N, 4·98. $C_{16}H_{13}O_4N$ requires C,67·8; N,4·95.)

The 2-nitro fluorene-9-carbinol acetate was hydrolysed by boiling with 50% dilute hydrochloric acid during 24 hours. The product was extracted with benzene and placed on a silica column and eluted with benzene. When no further product appeared,the column was washed through with alcohol giving the nitro-carbinol as a pale yellow solid, in the form of fine micro-needles melting at 117°

(Found: C, 71·03; H, 4·9; N, 5·4. $C_{14}H_{11}O_3N$ requires C, 70·8; H, 4·6; N, 5·4.)

The carbinol was refluxed with phosphorous pentoxide in xylene during two hours, and the product purified by chromatography through a short alumina column in benzene.

This gave a product in the form of long pale-yellow prisms melting at 102°. The literature gives 99° as the melting point for 2-nitrophenanthrene but this is obtained by a long and tedious crystallisation of the nitration products of phenanthrene. The 2-nitro derivaive,being one of the more soluble, is particularly hard to obtain pure and the figure 99° probably represents a product somewhat contaminated by other isomeric forms. The product obtained, against such 2-nitrophenanthrene, gave no depression of the melting point. On oxidation with chromic acid in acetic acid,it gave a product melting at 258°, identical with the product obtained on nitrating phenanthrenequinone, 2-nitrophenanthrenequinone, (m.pt. 257°).

The quinone on warming with 10% caustic soda for twenty minutes at 65°,with vigorous stirring,gave the hydroxy acid; which, on oxidation with potassium dichromate in dilute sulphuric acid, gave 2-nitrofluorenone. This was insoluble in neutral solvents. It was

isolated by adding ferrous sulphate to the reaction mixture, followed by dilute sodium hydroxide. The solution was then taken to dryness, and the residue sublimed in vacuo in a micro-sublimation apparatus. The product was obtained as a pale golden sublimate melting at 220° (lit.220°). It was identical with 2-nitrofluorenone obtained by oxidation of 2-nitrofluorene.

The yield of 2-nitrofluorenone from 100 mgm., of fluorene-9-carbinol was about 40 mgm., or about 80 - 85% per stage.

Preparation of 2-nitrophenanthraquinone and 2 nitro fluorenone.

The 2-nitrophenanthraquinone and 2 nitrofluorenone obtained by the reaction series, were compared with these two compounds prepared in bulk by methods already in the literature.

2 Nitrophenanthraquinone.

Phenanthraquinone (30 gms) was dissolved in concentrated nitric acid (200 c.c.) and heated to boiling. The mixture was boiled for two minutes and then poured into water. The resulting precipitate was filtered off and crystallised from acetic acid.

The product melted at 257°. (Schmidt and Austin[82]).

2 Nitrofluorenone.

30 gms. of the previously prepared 2-nitrofluorene were powdered, and refluxed with acetic acid (300 c.c.) and sodium dichromate (102 gms.) After one hour, the solution was cooled and filtered. The residue consisted of yellow crystals melting at 218°. They were almost pure as obtained, but could be further purified by crystallising from acetic acid or by sublimation.

The synthesis was repeated from fluorene using isotopic materials. Runs were carried out as detailed before, beginning with barium carbonate (100 mg.) and proceeding as far as the fluorene - 9 - carbinol stage. In all, twenty such runs were carried out from a total of 2 gms. of barium carbonate-^{13}C. This process being used since the apparatus used had been designed for runs of about 100 mgm., and at such a level the synthesis was familiar, and, mainly, to protect against accidental loss of $^{13}CO_2$.

The resulting fluorene - 9 - carbinol (600 mgm) was dissolved in ice-cold acetyl chloride and taken to dryness. The resulting acetate was washed with ice water and redried. It was then dissolved in ice-cold acetic anhydride (6 c.c.) and the solution treated dropwise with vigorous stirring with a previously prepared mixture of 0·18 c.c. concentrated nitric acid in acetic anhydride (6 c.c.) and acetic acid (6 c.c.)

maintaining the temperature at 0° C. The product was stirred for a further hour. Ice water was added and stirring continued for a further hour. The mixture was extracted with benzene and the benzene extract placed on top of a silica gel column and eluted with benzene. The eluate was taken to dryness and boiled with 50% hydrochloric acid for 24 hours. The product was purified as before and refluxed with xylene (20 c.c.) and phosphorous pentoxide (2 gms). The hydrocarbon was decanted from the residual phosphorous pentoxide and chromatographed through an alumina/activated charcoal column. The yield of 2-nitrophenanthrene from barium carbonate (2 gms) was about 500 mgms or about 22%, representing, for the eight stages between barium carbonate and 2-nitrophenanthrene, a yield of 87% average.

50 mgm. of the 2-nitrophenanthrene so obtained, were oxidised to the corresponding quinone, re-arranged to the hydroxy acid, and finally oxidised to 2-nitrofluorenone which was oxidised to carbon dioxide as detailed previously. The remainder of the 2-nitrophenanthrene was used a) for the selective splitting of the molecule by vanadium pentoxide oxidation to determine the ^{13}C ratio across positions 9 and 10 before the benzilic acid re-arrangement stage. b) For reduction to amino-phenanthrene and hence by diazotisation to give 2-chloro, 2, bromo, and

2-iodo phenanthrenes, (Bachman and Boatner[83]) and also 2-methoxyphenanthrene and 2 phenanthrol.

Vanadium Pentoxide Oxidations

Phenanthrene has been oxidised, mainly to phthalic anhydride, by vapour phase oxidation with air over a vanadium pentoxide catalyst heated at 400° [90]. 2-nitrophenanthrene (100 mgm.) was weighed into a silica boat, this was then introduced into a silica tube packed with vanadium pentoxide heated at 450°. A slow stream of preheated oxygen was passed over the boat which was gently heated to the vaporisation point of the 2-nitrophenanthrene. The products were collected in a U-tube cooled in ice. The tube was washed out with acetone and the extract taken to dryness. The product was dissolved in benzene and placed on top of a silica column and eluted with benzene, after 30 c.c. of benzene had been collected the column was washed out with acetone. The residue was mainly unattacked 2-nitrophenanthrene and was purified further by passing it through an alumina/norite column in benzene, when it was obtained melting at 98°. The acetone eluate was taken to dryness and sublimed to purify it from 2-nitrophenanthrenequinone and tarry impurities. It was then re-chromatographed through a silica column inacetone and was obtained as long pale yellow needles melting at 116°, (lit. 119° (114°)).

The yield of anhydride obtained from 2-nitrophenanthrene (100 mgm.) was about 10 mgm., the yield varying largely, dependant on rate of oxygen flow, time of contact, rate of vaporisation, etc. The main impurity was unattacked nitrophenanthrene, of which about 60 mgm. were recovered. The yield of anhydride on 2-nitrophenanthrene used, being about 25%. The 2-nitrophenanthrene was reduced by the normal tin and hydrochloric acid method, and 100 mgm. of the resulting amino-phenanthrene oxidised. The phthalic anhydride obtained was purified as for the 2-nitro compound, and obtained as long colourless needles melting at 130° (lit. 131·6). The benzene eluate contained a rather impure 2-amino-phenanthrene which was difficult to purify, together with, apparently, some naphthalene, and was rejected. The yield of phthalic anhydride was 40%.

The 4-nitrophthalic anhydride and phthalic anhydride were submitted to the wet combustion method of Van Slyke, and the resulting carbon dioxide assayed.

2-Amino-phenanthrene Series.

About 50 mgms. of the 2-nitrophenanthrene were not reduced to the 2-amino compound but were oxidised to give 2-nitrophenanthrenequinone. The nitro-quinone was reduced to 2-aminophenanthrenequinone. (Brass and

Ferber[84]) by shaking with excess aqueous sodium hydrogen sulphide. It was then submitted to the benzilic acid re-arrangement followed by oxidation to the 2-aminofluorenone, etc., as before, with assay of the carbon dioxide samples.

2-Halo-phenanthrenes, 2 Phenanthrol and 2 Methoxy-phenanthrene.

The remaining 2-aminophenanthrene was diazotised (Bachmann and Boatner[83]).

In a typical run, sodium nitrite (300 mgms.) was dissolved in a cold mixture of water (1.5 c.c.) and concentrated sulphuric acid (3 c.c.). The mixture was warmed gently to give a clear solution, and then cooled to 0° with rapid stirring. A solution of 2-aminophenanthrene (400 mgm.) in pyridine (2 c.c.) was then added dropwise during one hour, the solution was stirred for a further hour and then diluted with ice-water to 40 c.c. Urea (0·2 gms.) in water (5 c.c.) was added and the mixture stirred for a further hour.

2-Phenanthrol.

15 c.c. of the solution of phenanthrene diazonium sulphate were diluted to 30 c.c. and heated at 100° for one hour. The precipitated phenanthrol was extracted with ether, the ether extract was extracted with dilute caustic soda. The caustic soda extract was then acidified and extracted with ether. The yield

obtained on a 1 gramme scale was about 30%. The yield from the above was divided in half. One part was subjected to the benzilic acid re-arrangement followed by oxidation etc. as before. The 2-hydroxy fluorenone obtained was insoluble in ether and was purified by sublimation. The remaining phenanthrol wasmethylated by shaking with dimethyl sulphate in dilute caustic soda. The product was purified by chromatography through a short alumina column and submitted to the benzilic acid re-arrangement etc as before.

The remainder of the diazo-solution was divided into three.

1. 2-chlorophenanthrene.

To excess of a solution of mercuric chloride (1.0 gm.) and potassium chloride (1·0 gm.) was added to the solution of the diazo salt. The resulting precipitate of the double salt after standing for one hour was filtered, washed with water and air dried. The solid was covered with a layer of potassium chloride and gently heated under reduced pressure, the resulting chlorophenanthrene being collected on a "cold finger". The solid product was dissolved in benzene and purified by chromatography on a short alumina column, giving 2-chlorophenanthrene melting at 86°. This was oxidised to the quinone etc. as before.

2. 2-bromophenanthrene.

The solution of the diazonium salt was treated as for the chloro-compound using mercuric and potassium bromides. The product melted at 95°.

3. 2-iodophenanthrene.

The third part of the diazo solution was treated with excess potassium iodide in water. The product was allowed to stand overnight. The solution was then boiled until no further nitrogen was evolved, and, after cooling, extracted with benzene and chromatographed. The product melted at 112° (lit. 116°) and on oxidation gave a quinone melting at 220° (lit. 223°) which was treated as before.

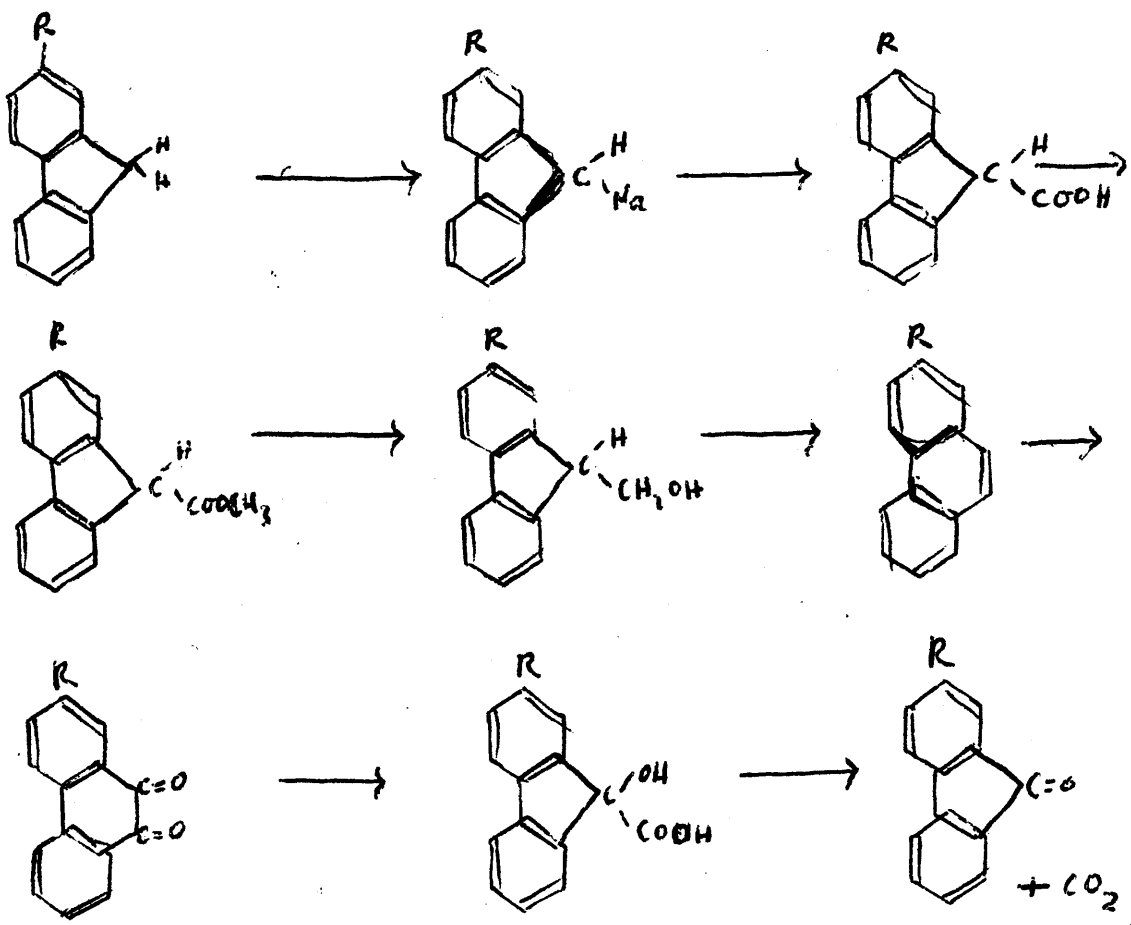
The benzilic acid re-arrangement had now been effected on 2-nitro, 2-amino, 2-hydroxy, 2-methoxy and 2-chloro, bromo and iodo phenanthrenequinones, all with a known C^{13} ratio across positions 9 and 10. By selective oxidation the ratio across C_9 and the carboxylic acid carbon of the various substituted fluorene-9-hydroxy-9-carboxylic acids was obtained.

To study the mechanism of the Wagner re-arrangement involved in the ring enlargement stage from the fluorene-9-carbinol to phenanthrene further, the synthesis was effected from the beginning with 2-methoxy, 2-chloro, bromo and iodo fluorenes, all obtained from 2-amino

fluorene. Since the distribution at the benzilic acid stage for the corresponding phenanthrenequinones is known from the preceding results, the distribution at the Wagner stage could be calculated.

For interest sake the synthesis was also completed with 2 methyl and 2 ethyl fluorenes, but the results are more difficult to interpret, since the relative distributions at the Wagner re-arrangement and benzilic acid re-arrangement stages can only by suggested.

All these syntheses were effected by the following straightforward synthesis beginning with the appropriate substituted fluorene:-



2 Bromo series

2 bromo-fluorene was prepared, by the method of Bachmann and Boatner for the preparation of-2 bromo-phenanthrene, from 2-amino fluorene. The amino fluorene was prepared by reduction of 2-nitro fluorene with zinc and ethyl alcohol.

2-bromofluorene-9-carboxylic acid - C_{10}-C^{13}.

Each series was, as far as possible, carried out by the standard scheme worked out for the unsubstituted series.

In a typical run, triphenylmethyl sodium was prepared from sodium (80 mgm.) ether (3·5 c.c.) and triphenylmethyl chloride (220mg.). To the resulting sodiotriphenylmethyl, the fluorene compound (1 m.mole) was added and the orange product carbonated with the carbon dioxide derived from 100 mgm. of barium carbonate-C^{13} (66% C^{13}). The resulting acid in the present series had a melting point 215 - 217°.

The acid was methylated with excess diazomethane, the resulting ester, after purification by chromatography, melted at 82°. On reduction with lithium aluminium hydride it gave 2-bromo-fluorene-9-carbinol (m.pt. 80°). This was compared with carbinol obtained when 2 bromo-fluorene was condensed with ethyl formate in the presence of potassium methoxide, and the resulting 2 bromo-9 formyl fluorene reduced with formalin. The product

melted at 82° and gave, on heating with phosphorous pentoxide, 2 bromo-phenanthrene. The carbinol obtained above was treated with phosphorous pentoxide in xylene as before. The product after purification on an alumina/norite column melted at 95° . This on oxidation gave a quinone melting at 228° (lit. 233°) which, on warming at 80° with 10% caustic soda for thirty minutes, gave an acid melting at 210° (lit. 213°). This on mild oxidation and purification of the product by passage through an alumina column gave 2 bromo-fluorenone m.pt. 147° (lit. 149) which was identified with the product obtained by direct oxidation of 2-bromo-fluorene. The carbon dioxide samples were collected and assayed as before.

2 Chloro and 2-iodo fluorene.

These were prepared from 2-amino fluorene by standard diazotisation techniques based on the paper by Bachmann and Boatner for the preparation of the corresponding phenanthrene compounds.

2-chlorofluorene	m.pt. 97°	lit. 97°
2 iodofluorene	m.pt.125°	lit. 125·5°

The series were carried through as for the 2 bromo series. No attempt was made to isolate the intermediate compounds these being characterised only at the phenanthrene and fluorenone stages.

2-chlorophenanthrene	m.pt. 83°	lit. 86°
2-iodophenanthrene	m.pt. 115°	lit. 116·5°
2 chlorofluorenone	m.pt. 124°	lit. 125·6°
2-iodo fluorenone	m.pt. 140°	lit. 142°

2 Methyl and 2 ethyl series.

2 Methyl fluorene was prepared by reduction of 2-formyl fluorene, obtained by a standard Gatterman aldehyde synthesis (Hinkel, Ayling and Beyman[85]).

Fluorene (25 gms.) chlorobenzene (100 c.c.) hydrogen cyanide (24 c.c.) and aluminium chloride (60 gms.) were reacted according to the procedure of Hinkel, Ayling and Beyman, to give a yield of 22 gms. of 2-formyl fluorene isolated via its bisulphite compound.

To zinc (20 gms.), amalgamated by standing with aqueous mercuric chloride (5% 40 c.c.) for one hour, 2-formyl fluorene (5 gms.) and hydrochloric acid (1 part concentrated acid : 2 parts water) (40 c.c.) were added. The mixture was refluxed for eight hours until the zinc had all dissolved. The mixture was diluted and steam distilled to give 2-methyl fluorene (1 gm.) which was crystallised from aqueous alcohol. m.pt. 102°

The methyl fluorene was carbonated as before to give 2 methyl fluorene-9-carboxylic acid m.pt. 210°

This was esterified with diazomethane to give the methyl ester m.pt. 106° which on reduction followed by ring enlargement gave 2-methyl phenanthrene m.pt. 56° which was oxidised to the quinone m.pt. 148° on which the re-arrangement etc. was effected. The final product was 2-methyl fluorenone which was identified against the same compound obtained by oxidation of 2 methyl fluorene.

2-Ethyl fluorene.

2-Ethyl fluorene was prepared by reduction of 2-acetyl fluorene prepared by a standard Friedel Crafts reaction from acetic anhydride and fluorene.

(Ray and Rieveschl[86]).

Fluorene (80 gms.) is acetylated by acetic anhydride (49·4 gms) in the presence of aluminium chloride (128 gms.) and carbon disulphide (350 ml.) according to the method of Ray and Rieveschl. The isolated acetyl fluorene m.pt. 124° was then reduced with amalgamated zinc and the 2-ethyl fluorene isolated by steam distillation according to the procedure given above for 2 methyl fluorene.

The product m.pt 81° was carbonated, esterified, and reduced as before. The Wagner re-arrangement gave a product melting at 64°. On completing the synthesis 2-ethylfluorenone was obtained which after purification by chromatography and sublimation

melted at 127°. It was identified against the same product m.pt. 128° obtained by oxidation of 2-ethyl fluorene.

2 Methoxy fluorene.

2-hydroxy fluorene was prepared by hydrolysis of fluorene diazonium sulphate prepared from 2-amino fluorene and the product was methylated by shaking with caustic soda and dimethyl sulphate. The product melted at 107°.

The 2 methoxy fluorene was submitted to the standard series giving a phenanthrene derivative m.pt. 101° , a quinone melting at 169° and a fluorenone melting at 75°.

Benz-(b) fluorene series.

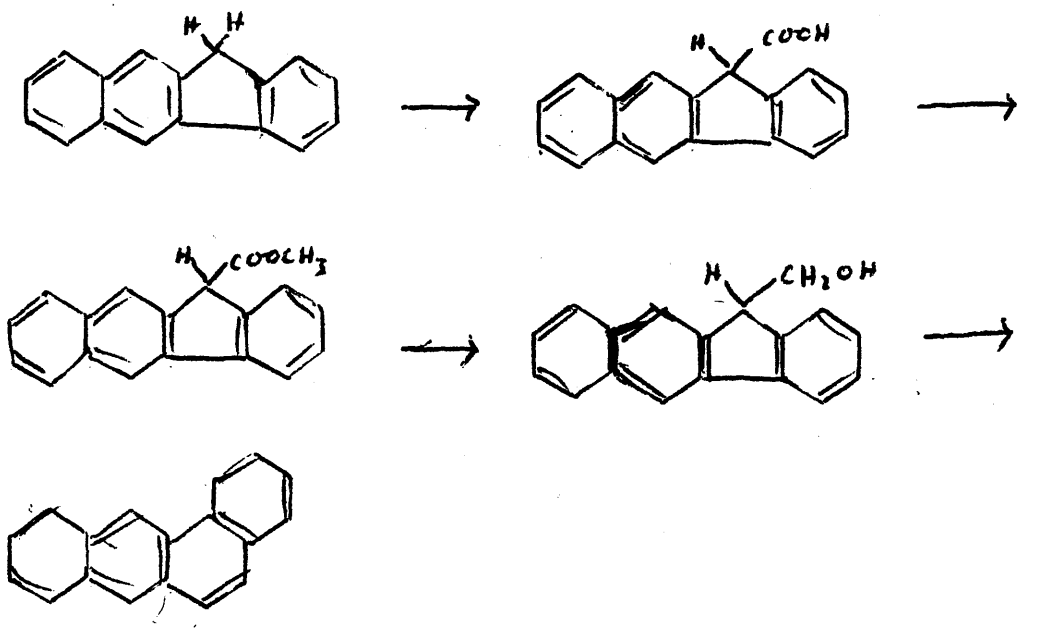
Cinnamic acid was reduced with sodium amalgam to give phenylpropionic acid, the yield is quantitative. To the phenylpropionic acid (50 gms.) is added phosphorous pentachloride (69 gms) gradually. The resulting yellow liquid is distilled and after an early fraction of phosphorous oxychloride, the phenylpropionic chloride was distilled under reduced pressure (12 m.m. Hg.). The resulting chloride (25 gms) was dissolved in petroleum ether 60-70 (40 gms) and aluminium chloride (25 gms) added. The mixture was then heated gradually until the initial vigorous reaction

had subsided. Water was added cautiously and the mixture steam distilled, the distillate was separated, washed with sodium carbonate solution and finally with water, dried over calcium chloride and distilled. Yield 10 gms. (Kipping[87]).

Hydrindone (10 gms.) and o-phthalaldehyde 10 gms, were heated under reflux and 25 c.c. of a 28% solution of potassium in methyl alcohol were added dropwise during half an hour. The product was cooled and filtered and the residue recrystallised from alcohol. Yield 11 gms. (Thiele and Wanscheidt[88]).

The resulting benzo (b) fluorenone was reduced by a standard Clemmensen reduction to benzo (b) fluorene.

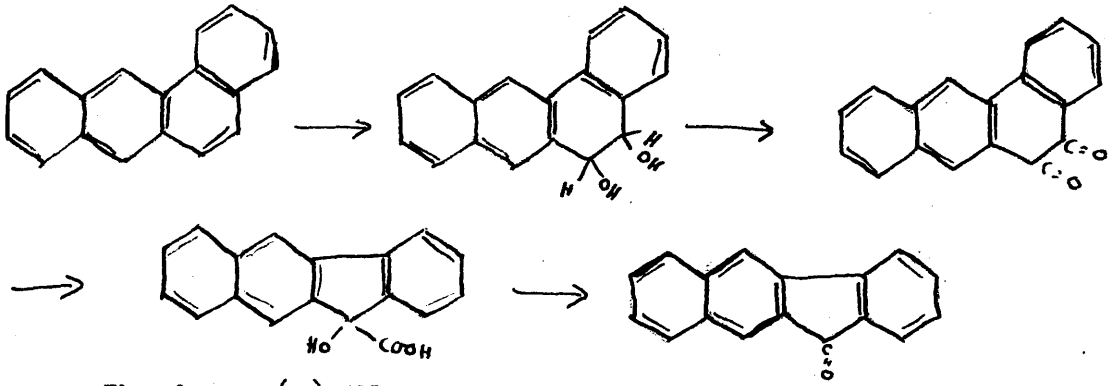
The following series was then conducted:-



The details are as follows:-

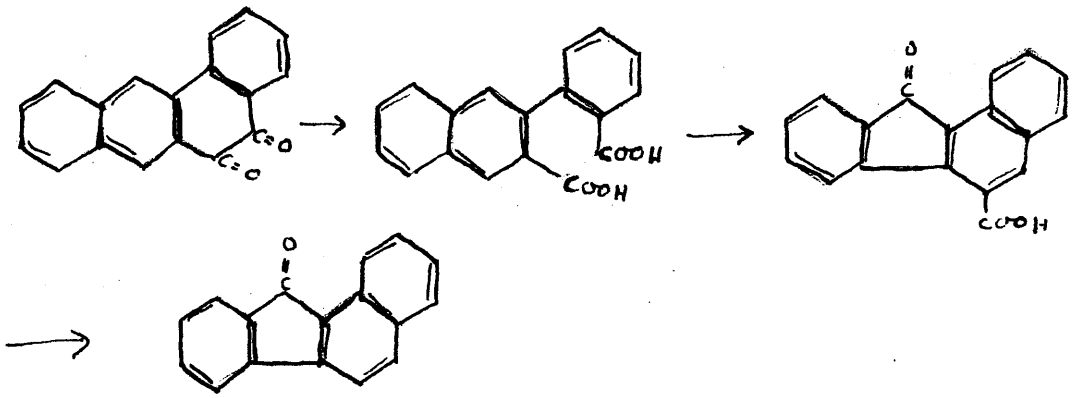
Sodio-triphenyl methyl, prepared as before from 220 mgs. of triphenyl methyl chloride, was treated with 216 mgs. of (b) benzfluorene to give a deep-purple product which was carbonated with the carbon dioxide from 100 mgs. of barium carbonate $-^{13}C$. The acid was isolated as before and treated with excess diazomethane in ether, the residue on evaporation was treated with excess of a lithium aluminium hydride slurry in ether and the carbinol isolated as before. Xylene (10 c.c.) and Phosphorous pentoxide were added and the mixture refluxed. The hydrocarbon layer was decanted through a short alumina/norite column and the eluate taken to dryness. The resulting (a) benzanthracene melted at 156°. The benzanthracene was dissolved in benzene (6 c.c.), osmium tetroxide (0·2 gm) was added and the mixture shaken with the addition of a drop or two of pyridine, for one hour, and allowed to stand 48 hours. 10 c.c. of methylene dichloride and 3% potassium hydroxide (15 c.c.) containing 1·5 gm of mannitol were then added, the mixture was shaken for five hours and then separated. (Cook and Schoental[89]) The organic layer was taken to dryness and treated with acetic acid/chromium trioxide and the product poured into water, and the resulting quinone filtered off.

50 mgms. of the quinone were subjected to the re-arrangement and oxidation as before.



The benz (a) fluorenone was oxidised by the wet-combustion method to carbon dioxide, and the carbon dioxide sample assayed as before for ^{13}C enrichment.

The following synthesis was carried out on the remainder of the quinone to determine the ^{13}C enrichment across the ketonic groups in the benzanthraquinone.



The remaining quinone (70 mg.) was dissolved in acetic acid (7 c.c.) and to it was added a few drops of 30% hydrogen peroxide and it was heated on the steam bath for one hour, a further addition of hydrogen peroxide was made, and the product allowed to stand

overnight, taken to dryness and extracted with bicarbonate during 24 hours. The product was filtered and the filtrate acidified. The precipitated acid was filtered off and treated with 4 c.c. of concentrated sulphuric acid. This was accomplished by collecting the precipitate on a filter stick and placing the stick in sulphuric acid. After two hours the sulphuric was cooled and diluted with ice water and filtered off through the filter stick. Toluene was added and heated to boiling and then sucked through the stick, the resulting filtrate was taken to dryness. The residue was treated with quinoline (2 c.c.) and basic copper carbonate (20 mgs) was added and the mixture refluxed for 15 minutes. The quinoline solution was filtered and diluted with dilute hydrochloric acid and extracted with benzene. The benzene solution was purified by chromatography and the resulting benzfluorenone collected directly into a tube for Van Slyke combustion, the resulting carbon dioxide being assayed as before for ^{13}C content.

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