This is to certify that Mr JOHN STOCKS FLANDERS has successfully sustained an oral examination on the subject matter of his thesis by a committee of the Department of Chemistry.

Members
of
Committee

May 1938.

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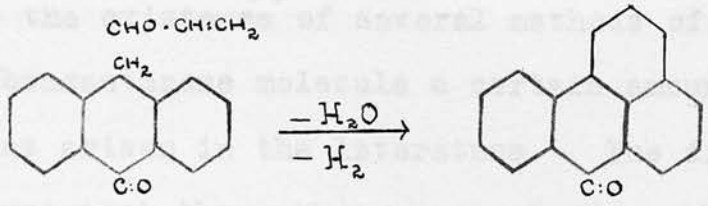
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INTRODUCTION

The study of the chemistry of benzanthrone and its derivatives has been, and still is being, extensively prosecuted. Apart from the purely academic interest of this work considerable importance attaches to these compounds in respect of their relation to the dibenzanthrone dyestuffs.

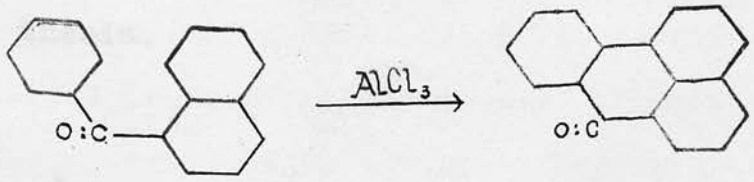
Benzanthrone itself was first prepared by Bally in 1905 (Ber., 1905, 38, 194) during the course of his investigations on the Skraup reaction with substituted anthraquinones. On heating anthraquinone with glycerol and sulphuric acid in the presence of a reducing agent Bally obtained benzanthrone. Since the original discovery this method of synthesis has been slightly modified, the anthraquinone being reduced to anthrone

by means of copper powder and sulphuric acid before the addition of the glycerol. Although several interpretations of the mechanism of this reaction have been put forward none has been completely accepted, there being some lack in each of a complete agreement with the experimental evidence. Broadly, however, the reaction undoubtedly involves a condensation between anthrone (I) and acrolein (formed from the glycerol and acid), followed by a loss of water and hydrogen to yield benzanthrone (II).



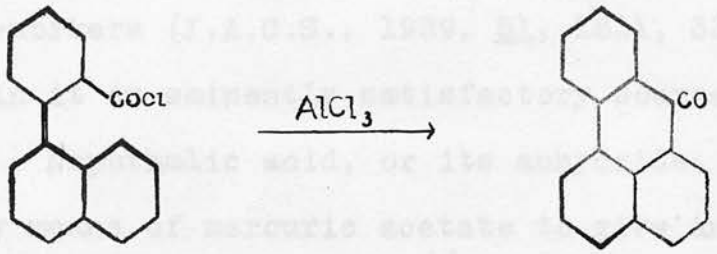
I II

A later synthesis, carried out by Scholl and Seer (Ann., 1912, 394, 111), involved "baking" α-benzoylnaphthalenes with aluminium chloride. This method, a process of aerial oxidation, also finds application in the synthesis of substituted benzanthrones.

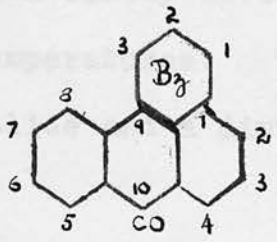


A third synthesis, which leaves no doubt as to the

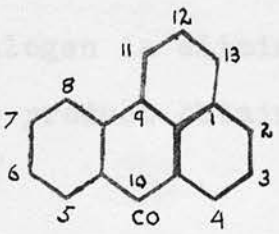
constitution of benzanthrone, is due to Schaarschmidt (Ber., 1918, 51, 1082). In this preparation the acid chloride of ortho-1-naphthylbenzoic acid is converted quantitatively into benzanthrone by treatment with aluminium chloride.



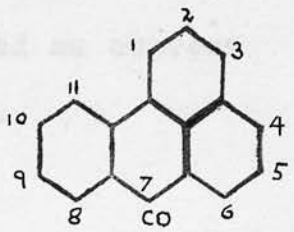
Due to the existence of several methods of numbering the benzanthrone molecule a certain amount of confusion has arisen in the literature. The first systems in use took the anthracene nucleus as their basis and are given below, (I) and (II), the latter still being employed in the Journal of the Chemical Society. The "International System" of nomenclature (III) which is used almost exclusively in the present day technical literature, and recommended by Heilbron (Dictionary of Organic Compounds), will be used throughout this thesis.



I

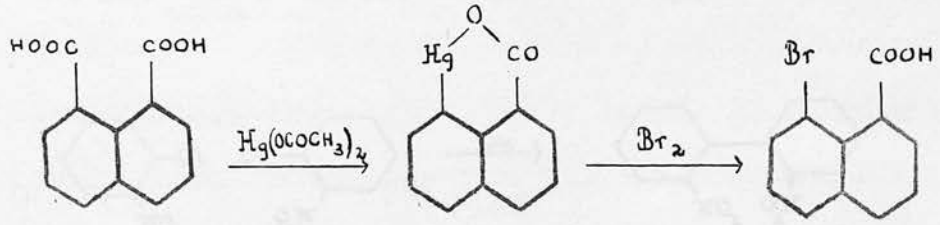


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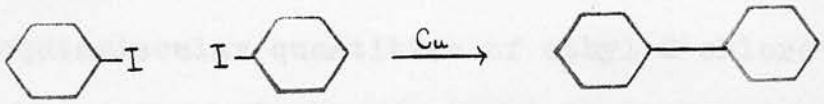
III

A modern method of wide applicability in the synthesis of benzanthrones utilises, as a starting material, certain peri-derivatives of naphthalene. During recent years the 8-halogeno-1-naphthoic acids have attracted considerable attention. Rule and co-workers (J., 1934, 170), employing the mercuration method of Whitmore and co-workers (J.A.C.S., 1929, 51, 1831, 3363), have found in it an eminently satisfactory source of the acids. Naphthalic acid, or its anhydride, is mercurated by means of mercuric acetate to give anhydro-8-hydroxymercuri-1-naphthoic acid. This compound, on treatment with bromine (or chlorine), yields the 8-halogeno-acid.

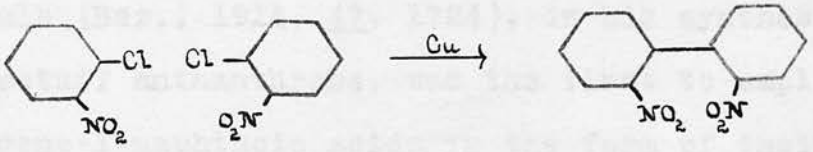


The importance of these acids in benzanthrone synthesis rests on their capability of taking part in the Ullmann reaction. This reaction, discovered by Ullmann in 1900 (Ber., 1901, 34, 2174; Ann., 1904, 332, 38), consists in treating halogenated aromatic compounds with finely divided copper ("copper bronze") at high temperatures. The halogen is eliminated as cuprous halide and a dinuclear product obtained.

Ullmann's investigations showed that the reaction proceeded smoothly with almost all iodo-compounds. For example, on heating iodobenzene with copper at 230°C in a sealed tube, diphenyl was formed.

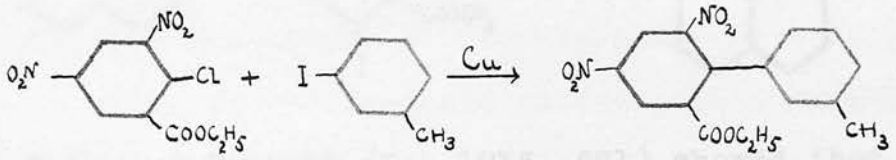


In the case of the corresponding bromo- and chloro-compounds, however, the halogen was found to be unreactive unless an increased lability was conferred upon it by the presence of other substituents in certain positions. Thus, o-nitrochlorobenzene readily underwent the reaction to give 2:2'-dinitrodiphenyl although the meta and para nitrochlorobenzenes were quite unreactive.

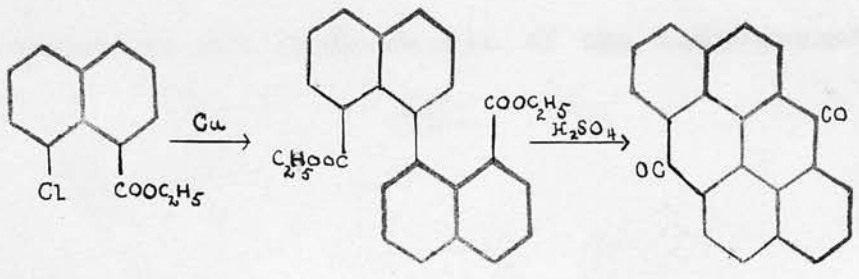


A carboxyl group in the ortho position has apparently an activating effect on the halogen similar to that of the nitro group. An important extension of the Ullmann reaction lay in the utilisation of mixtures of halogeno-compounds to yield unsymmetrical products. These products, more especially those substituted in such a manner as to exhibit stereoisomerism as a result of restricted rotation around the bond joining the phenyl

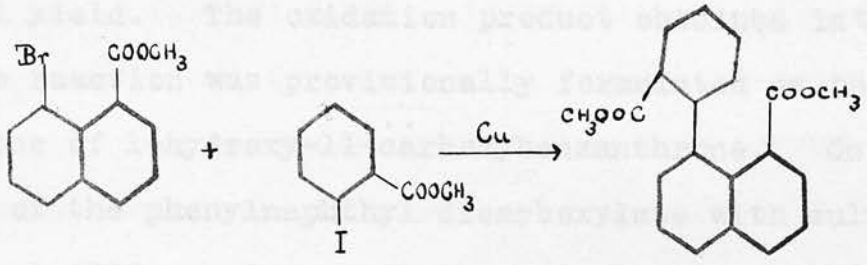
nuclei, have done much to stimulate interest in this phase of the Ullmann reaction. It has been demonstrated by Turner and co-workers that, in many cases, the yield of unsymmetrical product is surprisingly large. Thus Leslie and Turner (J., 1930, 1785) state that, when equimolecular quantities of ethyl 2-chloro-3:5-dinitrobenzoate and an aromatic iodo-compound are heated together in the presence of copper powder, ethyl 2:4-dinitrodiphenyl-6-carboxylates alone are formed. m-Iodotoluene, for example, gives a 68% yield of the unsymmetrical coupled product.



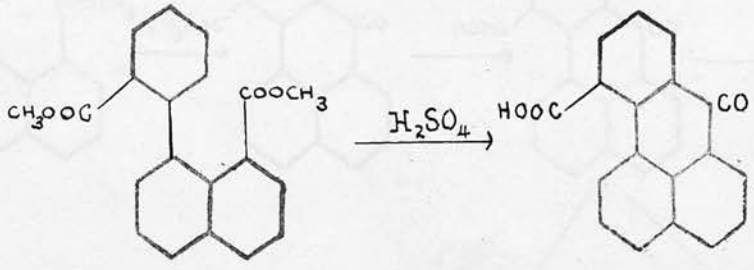
Kalb (Ber., 1914, 47, 1724), in his synthesis of the dyestuff anthanthrone, was the first to employ the 8-halogeno-1-naphthoic acids, in the form of their esters, in the Ullmann reaction. The ethyl ester of 8-chloro-1-naphthoic acid was treated with copper powder at 290°C, and the diethyl 1:1'-dinaphthyl-8:8'-dicarboxylate converted quantitatively to anthanthrone by the action of concentrated sulphuric acid.



Rule and Barnett (J., 1932, 2728), in an investigation of the reactivity of the bromine atom in 8-bromo-1-naphthoic acid, concluded that the halogens in methyl 8-bromo-1-naphthoate and methyl o-iodobenzoate were comparable in reactivity with one another. Barnett (Thesis, Edinburgh, 1932), on subjecting these two compounds to the Ullmann reaction at 190-200°C, was successful in obtaining a 40% yield of methyl 8-(o-carbomethoxyphenyl)-1-naphthoate.



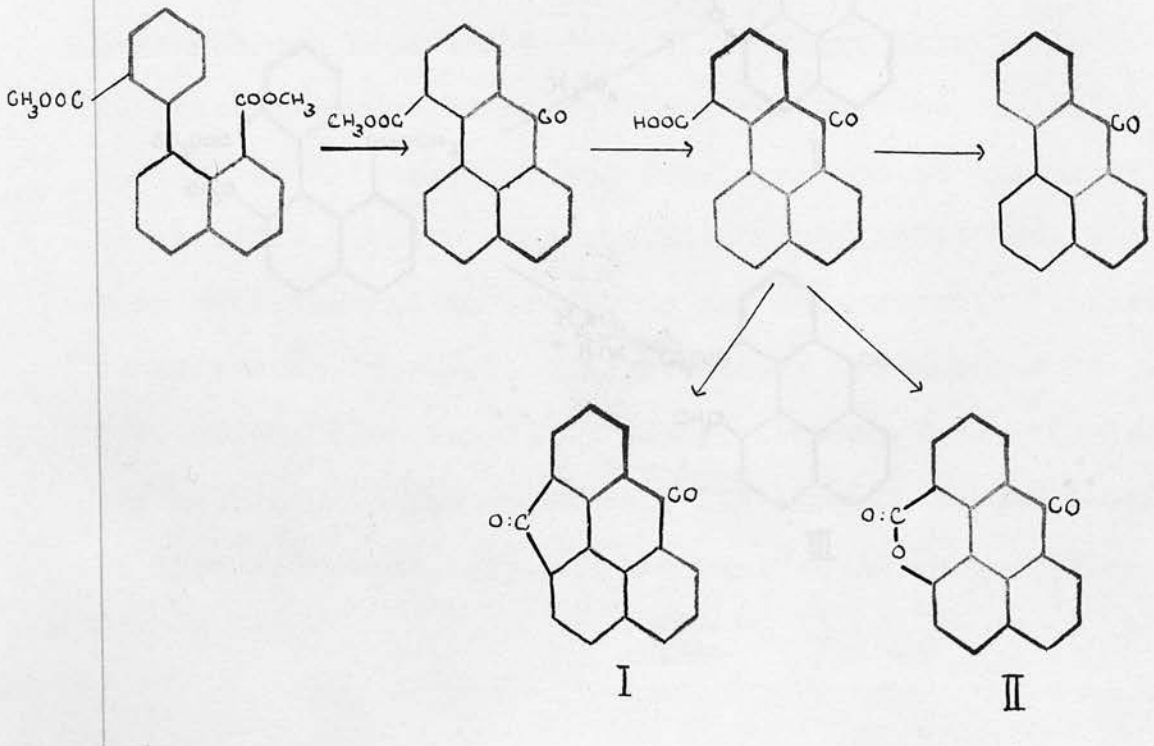
Rule and Pursell (J., 1935, 571) showed that the phenylnaphthyl dicarboxylate obtained by Barnett was, on treatment with concentrated sulphuric acid, converted quantitatively to 11-carboxybenzanthrone.



Barnett's preparation has since been examined more thoroughly and, by employing a lower temperature in the Ullmann reaction and using excess of the iodobenzoate,

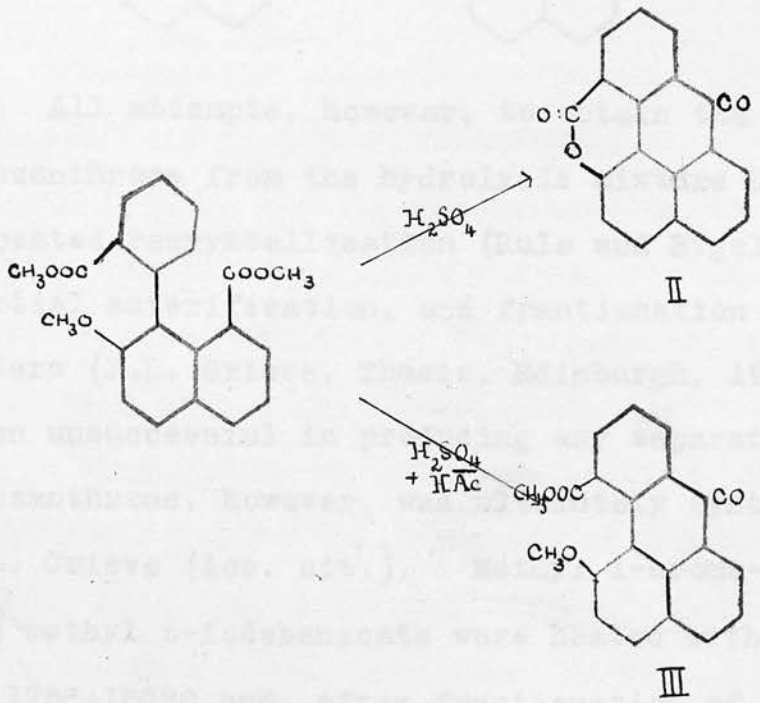
the yield of unsymmetrical product has been considerably increased (F.R. Smith, Thesis, Edinburgh, 1935).

Rule and Bigelow (J., 1935, 573), in an attempt to prepare 1:11-ketobenzanthrone (I) by a further cyclisation of 11-carboxybenzanthrone, showed that on more vigorous treatment of the acid with concentrated sulphuric acid a partial decarboxylation to benzanthrone took place. This was also accompanied by some oxidation, while the expected ketobenzanthrone was obtained only in very small yield. The oxidation product obtained in the above reaction was provisionally formulated as the lactone of 1-hydroxy-11-carboxybenzanthrone. On treatment of the phenylnaphthyl dicarboxylate with sulphuric acid at 50°C, an intermediate product, 11-carbomethoxybenzanthrone, was isolated. The scheme given below indicates the course of these reactions.



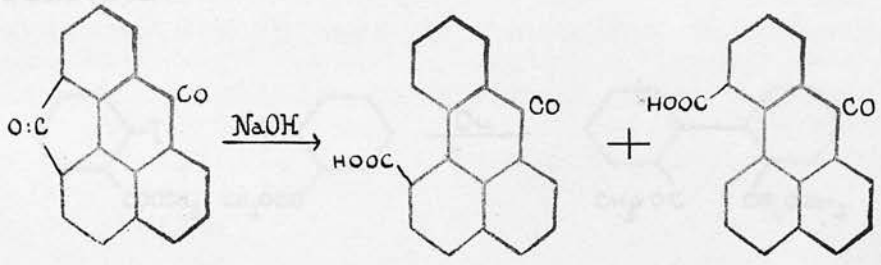
I II

The structure of the oxidation product (II) has been proved by a synthetic method (J.L. Grieve, Thesis, Edinburgh, 1936). Methyl 7-methoxy-8-bromo-1-naphthoate and methyl o-iodobenzoate when heated with copper powder at 175°C, gave a 46% yield of methyl 7-methoxy-8-(o-carbomethoxyphenyl)-1-naphthoate, and this unsymmetrical ester, on treatment with concentrated sulphuric acid at 100°C, gave the lactone of 1-hydroxy-11-carboxybenzanthrone (II). This compound is identical with the product obtained by the sulphuric acid oxidation of 11-carboxybenzanthrone. J.L. Grieve also prepared 1-methoxy-11-carbomethoxybenzanthrone (III) by cyclisation of methyl 7-methoxy-8-(o-carbomethoxyphenyl)-1-naphthoate with a glacial acetic acid - sulphuric acid mixture at 80°C.



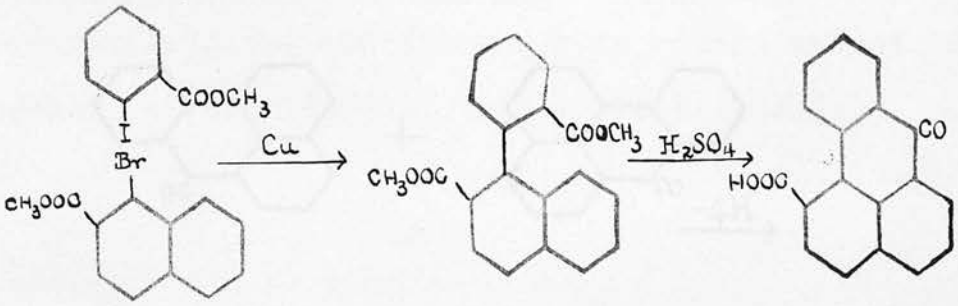
Although the yields of 1:11-ketobenzanthrone obtained by the action of sulphuric acid on 11-carboxybenzanthrone are poor, the compound was found to be readily prepared by the action of phosphorus pentoxide on a solution of 11-carboxybenzanthrone in molten phthalic anhydride at 200°C.

1:11-Ketobenzanthrone, when heated under reflux with dilute caustic soda solution, is slowly hydrolysed to give, presumably, a mixture of 1-carboxybenzanthrone and 11-carboxybenzanthrone (Rule and Bigelow, J., 1935, 574).

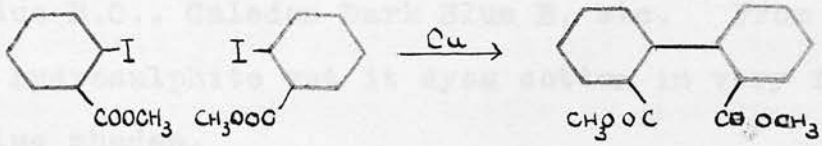


All attempts, however, to obtain the pure 1-carboxybenzanthrone from the hydrolysis mixture have failed. Repeated recrystallisation (Rule and Bigelow, unpublished), partial esterification, and fractionation of the mixed esters (J.L. Grieve, Thesis, Edinburgh, 1936) have all been unsuccessful in producing any separation. 1-Carboxybenzanthrone, however, was ultimately synthesised by J.L. Grieve (loc. cit.). Methyl 1-bromo-2-naphthoate and methyl o-iodobenzoate were heated with copper powder at 175°-180°C and, after fractionation of the coupling

product, and cyclisation with concentrated sulphuric acid, a 3% yield of 1-carboxybenzanthrone was obtained.

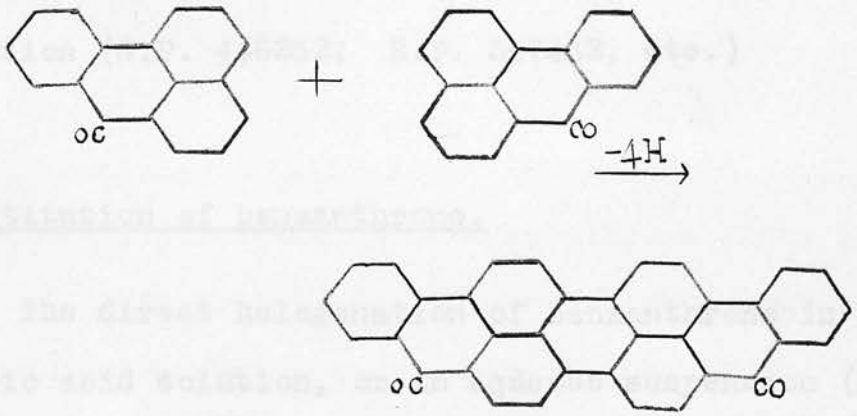


The small yield recorded in the above preparation was accounted for by the fact that a 90% yield of the diphenic ester was isolated from the reaction mixture. The formation of this compound therefore represents the main reaction.



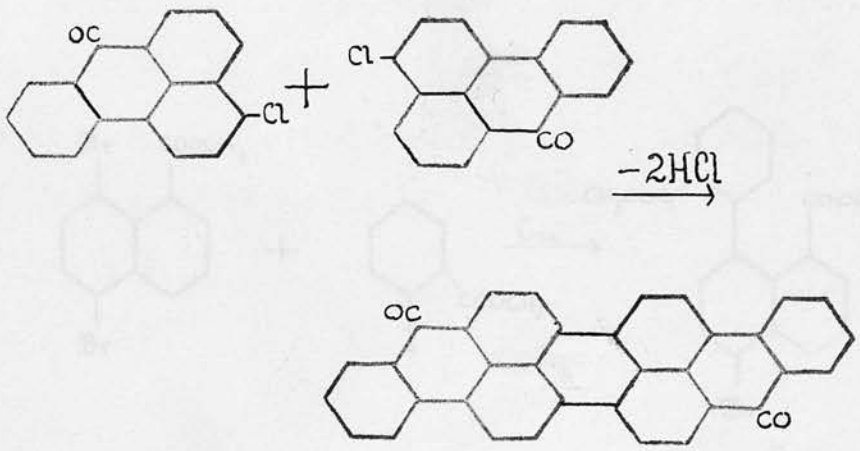
Technically benzanthrone is much utilised as an intermediate for the "Benzanthrone Colours". Benzanthrone itself, and its substituted derivatives, are not highly coloured compounds and are not used as vat dyes, doubts indeed being cast upon their capacity to form true vats with alkaline hydrosulphite. Bally, however, found that fusion of benzanthrone with caustic alkali at 230°-240°C led to the formation of a dark blue vat dye (Ber., 1905, 38, 195; G.P. 185221). This dye, a dibenzanthrone, has been shown by Scholl and Seer, (Ann.,1912,394,126) to have the structure indicated below, the union of the

two benzanthrone molecules occurring at the points 3 and 4.



This product, known commercially at first as Violanthrone, now appears on the market as Indanthrene Dark Blue B.O., Caledon Dark Blue B, etc. From a red-violet hydrosulphite vat it dyes cotton in very fast dark blue shades.

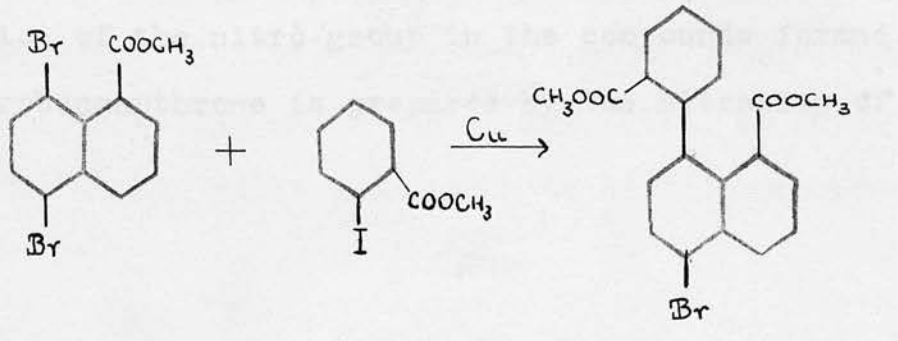
A symmetrical isomeride of dibenzanthrone, iso-dibenzanthrone, is the parent compound of a second class of dyes. Known also as Isoviolanthrone, it was originally prepared by the action of alcoholic potash on 3-chlorobenzanthrone.

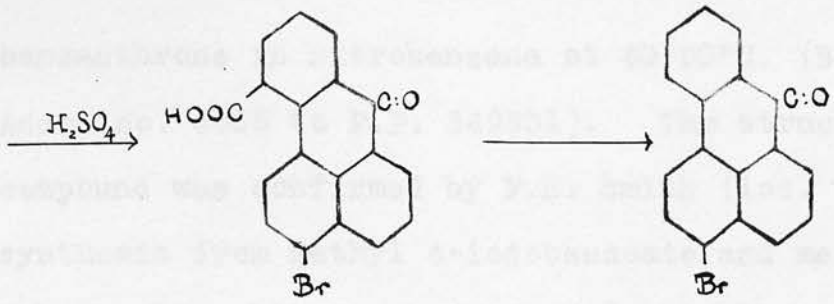


The action of alcoholic potash on the 3:3'-dibenzanthronyl sulphides and selenides is also productive of isoviolanthrone and forms a more recent method of preparation (G.P. 448262; B.P. 367462, etc.)

Substitution of benzanthrone.

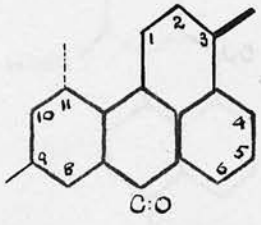
The direct halogenation of benzanthrone in glacial acetic acid solution, or in aqueous suspension (B.A.S.F., D.P. 193959; C., 1908, I, 1112), leads to the production of the 3-halogeno-derivatives. That the direct bromination product of benzanthrone was 3-bromobenzanthrone was conclusively proved by the work of F.R. Smith (loc. cit.) who subjected methyl o-iodobenzoate and methyl 5:8-dibromo-1-naphthoate to an Ullmann reaction. On cyclisation of the resulting phenylnaphthyl derivative with concentrated sulphuric acid and decarboxylation of the 3-bromobenzanthrone-11-carboxylic acid formed, 3-bromobenzanthrone was produced. This last compound was shown to be identical with that obtained by the direct bromination of benzanthrone.





According to Cahn, Jones and Simonsen (J., 1933, 444), the dichlorination of benzanthrone gives a mixture of isomeric 3:9- and 3:11-dichlorobenzanthrones. Dibromination, however, results in the formation of the homogeneous 3:9-dibromobenzanthrone (B.A.S.F., 1908, D.P. 193959).

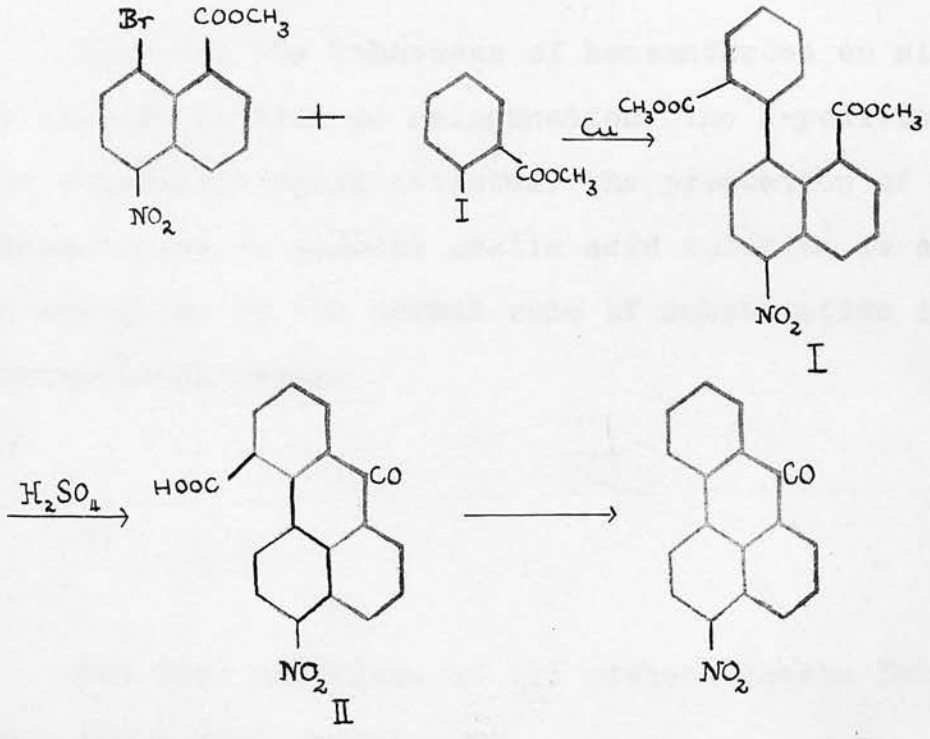
It is thus apparent that, while the halogenation of benzanthrone takes place primarily in the 3-position, the position 9 and, to a lesser extent, the position 11, are also open to attack.



Halogenation

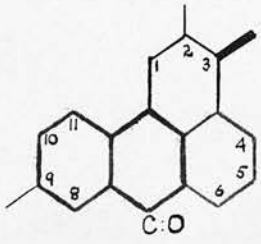
On nitration benzanthrone forms two mononitro derivatives, the conditions employed determining the position of the nitro-group in the compounds formed. 3-Nitrobenzanthrone is prepared by the nitration of

benzanthrone in nitrobenzene at 40-50°C. (B.A.S.F., Addn. no. 6435 to F.P. 349531). The structure of this compound was confirmed by F.R. Smith (loc. cit.) by its synthesis from methyl o-iodobenzoate and methyl 5-nitro-8-bromo-1-naphthoate by means of the Ullmann reaction, the cyclisation, as before, of the intermediate phenyl-naphthyl derivative (I), and the decarboxylation of the nitrocarboxybenzanthrone (II) formed.



When the nitration of benzanthrone is carried out in boiling glacial acetic acid an isomeric nitro-compound is produced. Believed for some time to be 9-nitrobenz-anthrone (Martinet and Drobatscheff, Chem. et Ind., 1929, 21, 227) it has since been shown to be 2-nitrobenzanthrone.

The dinitration of benzanthrone, or the further nitration of 3-nitrobenzanthrone, yields 3:9-dinitrobenzanthrone.



Nitration

Although the behaviour of benzanthrone on nitration is similar to that on halogenation, the 3-position, and the 9-position being attacked, the production of 2-nitrobenzanthrone in glacial acetic acid solution is apparently an exception to the normal rule of substitution in the benzanthrone series.

The work described in the present thesis falls into three main parts:

(a) the synthesis of 1:11-disubstituted benzanthrones, with special reference to the Ullmann reaction

(b) the examination of 1:11-disubstituted benzanthrones from a stereochemical viewpoint

and (c) a short account of the utilisation of chromatographic adsorption methods in the purification and separation of some benzanthrone derivatives.

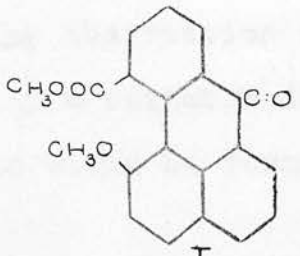
SUMMARY OF EXPERIMENTAL WORK AND DISCUSSION OF RESULTS.

I. THE SYNTHESIS OF 1:11-DISUBSTITUTED BENZANTHRONES WITH SPECIAL REFERENCE TO THE ULLMANN REACTION.

If a scale diagram or a scale model of a 1:11-disubstituted benzanthrone is examined it would appear that in this type of molecule a condition exists whereby the two substituting groups are held closely and rigidly together. For this reason it might be expected that the individual functional properties of the substituting groups would be modified or altered by the reciprocal influences of the groups themselves.

Prior to the work described in the present thesis only one true 1:11-disubstituted benzanthrone had been synthesised. This compound, 1-methoxy-11-carbomethoxybenzanthrone (I), was prepared by J. L. Grieve (J., 1937, 535). Its examination by the same worker re-

vealed the fact that it exhibited marked abnormalities in its reactions, the methoxyl group being found extremely sensitive to hydrolysing agents even under comparatively mild conditions.



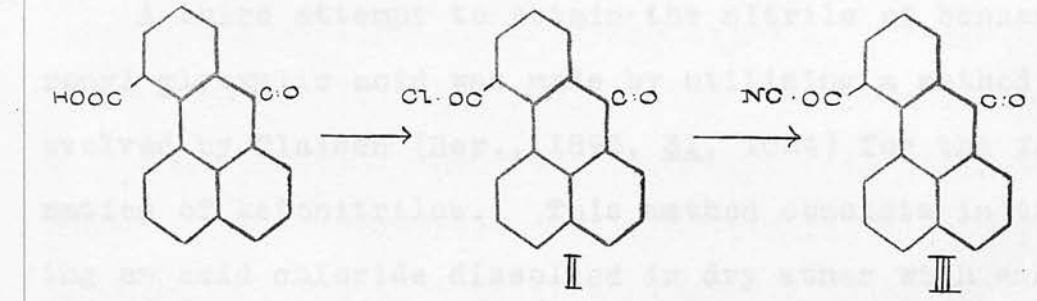
I

Grieve's work on 1-methoxy-11-carbomethoxybenzanthrone, which will be detailed fully below, lends support to the view that the 1:11-disubstituting groups in the benzanthrone molecule should exhibit peculiarities in their reactions, and forms a strong preliminary justification for work involving the synthesis and examination of this type of compound.

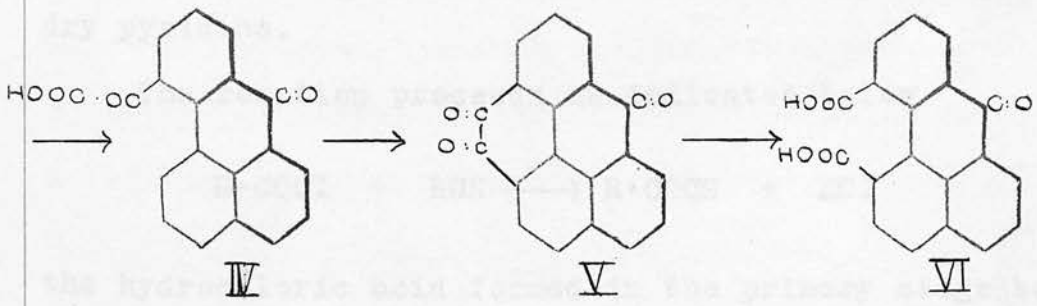
The Anhydride of 11-Carboxybenzanthrone.

In the present research an attempt was first made to synthesise 1:11-diketobenzanthrone (V) in the hope that on oxidation it would yield 1:11-dicarboxybenzanthrone (VI). The latter might then be treated as a starting material for further 1:11-disubstituted benzanthrones.

The line of approach to 1:11-diketobenzanthrone was as indicated below, attempts being made to prepare, from the acid chloride of 11-carboxybenzanthrone (II), the nitrile of benzanthronyl glyoxylic acid (III). This substance should yield, on hydrolysis, the corresponding acid (IV) and, by abstraction of the elements of water from this acid by a suitable dehydrating agent, 1:11-diketobenzanthrone would be formed.



II III



IV V VI

Several attempts were made to transform the acid chloride of 11-carboxybenzanthrone into the nitrile of benzanthronyl glyoxylic acid. The prolonged action of cuprous cyanide on the acid chloride in benzonitrile solution had apparently no effect, the bulk of the initial material being recovered in the form of the benz-

anthrone carboxylic acid.

The action of mercuric cyanide on the acid chloride in benzene solution, a standard method for the synthesis of ketonitriles, was productive of an almost quantitative yield of a neutral substance which did not contain nitrogen and hence could not be the desired nitrile. The constitution of this compound could not at first be determined. The results obtained in the following experiments, however, enabled its structure to be decided upon.

A third attempt to obtain the nitrile of benzanthronyl glyoxylic acid was made by utilising a method evolved by Claisen (Ber., 1898, 31, 1024) for the formation of ketonitriles. This method consists in treating an acid chloride dissolved in dry ether with anhydrous hydrogen cyanide and adding to this mixture pure dry pyridine.

The reaction proceeds as indicated below

$$R\cdot COCl + HCN \longrightarrow R\cdot COCN + HCl$$

the hydrochloric acid formed in the primary stage being removed by the pyridine. This reaction, productive of eminently satisfactory results in the hands of its discoverer, has since been used in many cases by later workers and is now accepted as a standard preparative method.

On its application to the present case, however, an 80% yield of a neutral nitrogen-free product was obtained

and found to be identical with that produced by the action of mercuric cyanide on the acid chloride.

Although none of the above methods had led to the desired result, namely the formation of the nitrile of benzanthronyl glyoxylic acid, the production of the same product by two different preparative methods demanded that its constitution be determined.

An analysis of the substance indicated that its carbon and hydrogen content approximated closely to that of the hitherto-unknown anhydride of 11-carboxybenzanthrone. Its neutrality also supported the view that this anhydride had been formed. That this supposition was correct was proved by the behaviour of the compound on treatment with an alcoholic solution of sodium ethoxide when equivalent amounts of the sodium salt of 11-carboxybenzanthrone and ethyl benzanthrone-11-carboxylate were produced. This reaction is characteristic of acid anhydrides.

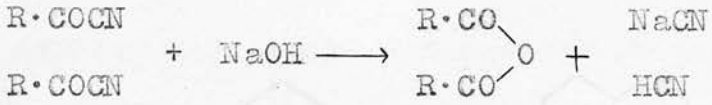
$$R\cdot CO\cdot O\cdot OC\cdot R \xrightarrow{NaOC_2H_5} R\cdot COONa + C_2H_5OOC\cdot R$$

Ethyl benzanthrone-11-carboxylate is not described in the literature and for purposes of identification had to be synthesised. It was prepared in excellent yield by treating the acid chloride of 11-carboxybenzanthrone with ethyl alcohol.

The work described above thus led to the surprising conclusion that the action of mercuric cyanide or of hydrogen cyanide on the acid chloride of 11-carboxybenzanthrone and the working up of the reaction product produced some change whereby the anhydride, and not the nitrile, was formed. Since the formation of the anhydride demands that certain quantities of water be present to transform a portion of the acid chloride back to the parent acid with subsequent interaction between acid or salt and acid chloride the experiment following Claisen's method was repeated but with extensive drying of the reagents employed. The ether, initially of high purity, was dried over sodium for several weeks; the hydrogen cyanide distilled through freshly-fused calcium chloride, and the pyridine dried over caustic soda and distilled. An almost quantitative yield of the anhydride, however, was once again obtained.

A complete explanation of the mode of formation of the anhydride cannot as yet be given but it would appear that the most probable answer to a rather baffling problem lies in assuming the initial production of an unstable ketonitrile or similarly constituted complex on treatment of the acid chloride with mercuric cyanide or hydrogen cyanide. The reaction product was then purified in all cases by extracting traces of 11-carboxy-

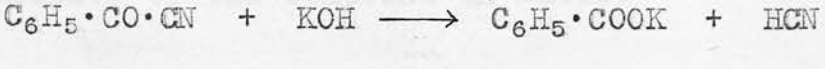
benzanthrone from it with dilute aqueous alkali, and it seems that, in this process, the unstable compound primarily formed may be decomposed to form the anhydride with a parallel production of hydrogen cyanide or of sodium cyanide.



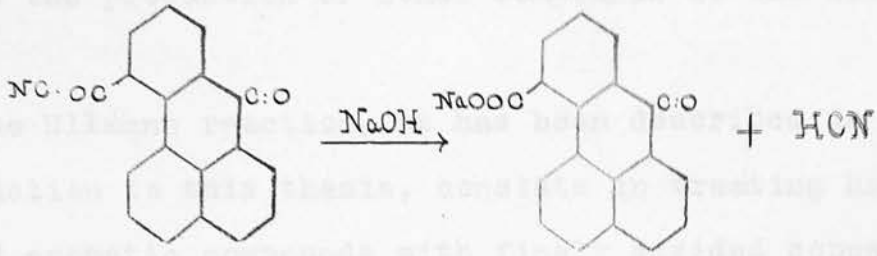
Such reaction does not normally occur but in the present case the anhydride is exceptionally insoluble in water and therefore not reactive to caustic soda.

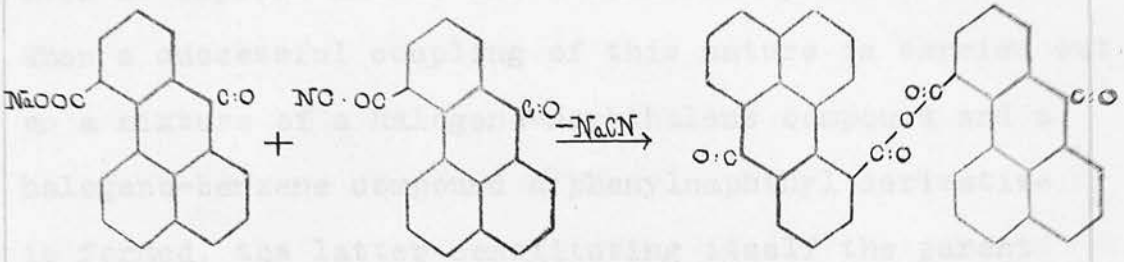
This possible interpretation of the mechanism of this reaction may rest on the lability of the ·CO·CN- grouping towards alkali, the link between carbonyl and ·CN- group having been shown relatively easy of rupture.

Thus Kolbe states that when the nitrile of phenylglyoxylic acid is treated with potassium hydroxide the potassium salt of benzoic acid and potassium cyanide are formed (A., 1854, 90, 62).



It is possible that a similar change takes place in the nitrile of benzanthronyl glyoxylic acid under brief contact with dilute alkali. The sodium salt of 11-carboxybenzanthrone which would be formed might then interact with the nitrile itself to produce the anhydride.





Whatever the explanation of the above change it would be unprofitable further to discuss it here.

The action of various hydrolysing agents on the anhydride was examined. It was found that concentrated sulphuric acid was probably the most rapid and effective agent while aqueous alkali had no effect even on boiling. This is in all probability due to the extreme insolubility of the compound in water.

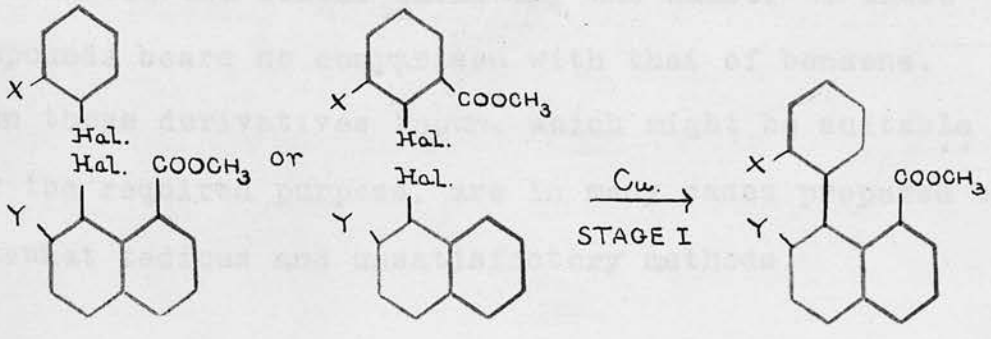
1:11-Disubstituted Benzanthrones and the Ullmann Reaction.

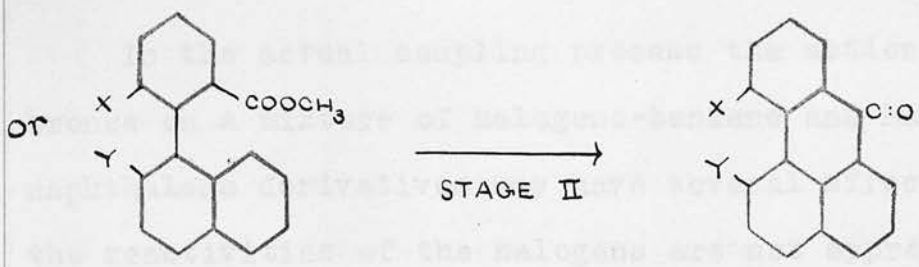
After the failure to prepare 1:11-dicarboxybenzanthrone by the methods described above attention was turned to the possible utilisation of the Ullmann reac-

tion in the production of other compounds of the desired type.

The Ullmann reaction, as has been described in the introduction to this thesis, consists in treating halogenated aromatic compounds with finely divided copper under suitable conditions when the halogen is eliminated as cuprous halide and a dinuclear product obtained. When a successful coupling of this nature is carried out on a mixture of a halogeno-naphthalene compound and a halogeno-benzene compound a phenylnaphthyl derivative is formed, the latter constituting itself the parent substance of a benzanthrone. Several typical examples of this are given in the introduction and serve to indicate that, of the various methods employed in benzanthrone synthesis, the Ullmann reaction is probably the one of greatest scope and utility.

In the synthesis of 1:11-disubstituted benzanthrones by this method several conditions must be fulfilled. Representing the 1:11-disubstituting groups in the benzanthrone molecule by the symbols X and Y a complete synthesis may be illustrated as below.





Briefly, the first stage involves the preparation of compounds suitable for participation in the reaction, the determination of conditions which will give a satisfactory yield of unsymmetrical product, and the separation of the latter from other substances formed in the reaction. The second stage consists in the cyclisation of the phenylnaphthyl derivative to the benzanthrone by a suitable reagent.

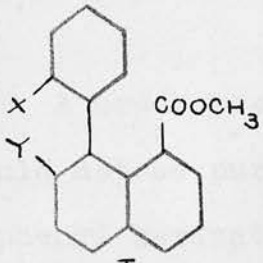
Before describing the present work it may be advisable to enumerate some of the difficulties which it was presumed might have to be encountered. The actual preparation of benzene derivatives of the required type was not expected to be difficult. In the case of the naphthalene derivatives, however, there is presented a very different state of affairs. Apart from the investigation of naphthalene compounds in special fields such as alkaloid and colour chemistry the number of these compounds bears no comparison with that of benzene. Even those derivatives known, which might be suitable for the required purpose, are in many cases prepared by somewhat tedious and unsatisfactory methods.

In the actual coupling process the action of copper bronze on a mixture of halogeno-benzene and halogeno-naphthalene derivatives may have several effects. If the reactivities of the halogens are not approximately balanced an exclusive coupling of one component of the mixture with itself may take place to give a diphenyl or a dinaphthyl derivative (See Rule and Smith, J., 1937, 1098; F. R. Smith, Thesis, Edinburgh, 1935), Even in cases, however, where this balancing of chemical reactivity is attained there is no absolute certainty that the Ullmann reaction will proceed in the desired direction while, on the other hand, instances have been noted where a wide divergence of the reactivities of the halogens involved have not rendered a successful coupling impossible.

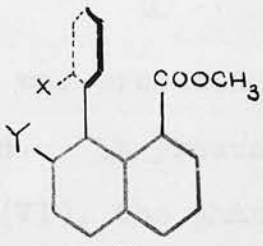
It appears that in addition to this balancing of halogen reactivities another factor, involving a steric hindrance effect, must be introduced; a factor, moreover, the occurrence of which it is impossible to predict, and the magnitude of which it is impossible to assess.

The second stage of the synthesis usually involves the abstraction of the elements of water or of methyl alcohol from the phenylnaphthyl derivative by a suitable reagent. In the majority of cases concentrated sulphuric acid at temperatures ranging from 50°C to 100°C

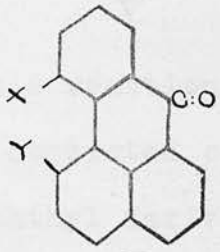
has been employed for this purpose. In addition to the possibility of sulphonation taking place under these conditions, however, another difficulty was expected to occur in the present work. In the case of a phenylnaphthyl derivative of the type (I)



I



II



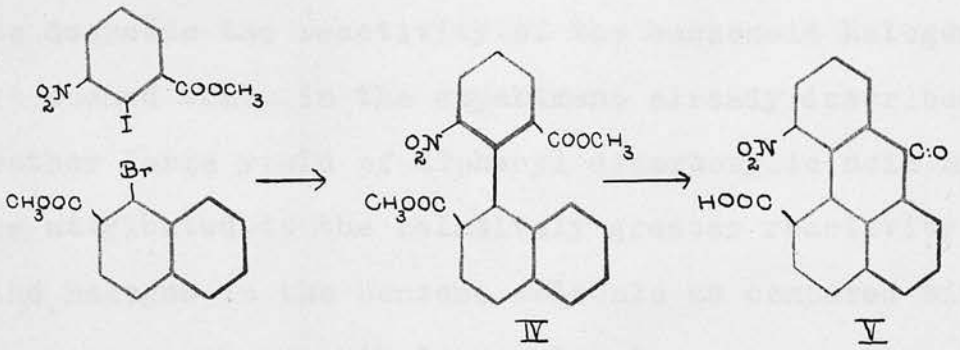
III

the blocking effect of the substituting groups X and Y will tend to give to the molecule a non-planar configuration as indicated in (II). In the formation of a benzanthrone, however, (III) the benzene ring and the naphthalene ring must fall into the same plane, a change which one would expect to be opposed strongly by the extremely close proximity of the groups X and Y in that new position.

How far the difficulties enumerated above were met with will now be described.

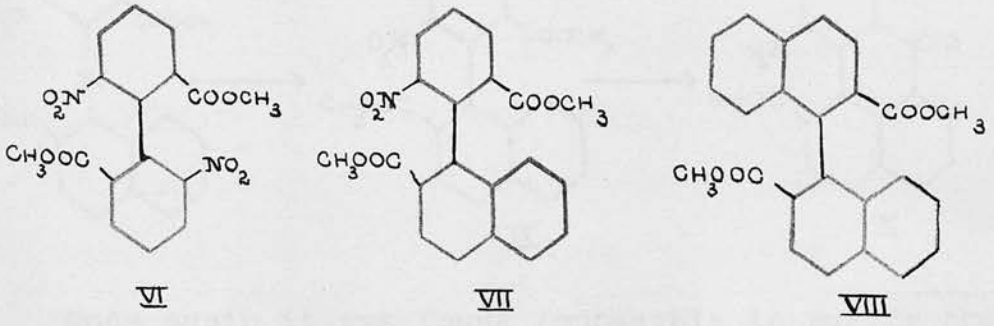
The first attempted synthesis of a 1:11-disubstituted benzanthrone in the present work was in the coupling of methyl 2-iodo-3-nitrobenzoate and methyl 1-bromo-2-naphthoate. It was hoped that these two compounds would link together to produce the phenylnaphthyl derivative (IV) from which, on cyclisation, 11-nitro-1-

carboxybenzanthrone (V) would be obtained.



IV V

A crude product was produced in this reaction which could not be purified. It presumably consisted of the diphenyl derivative (VI), the phenylnaphthyl derivative (VII) and the dinaphthyl derivative (VIII).



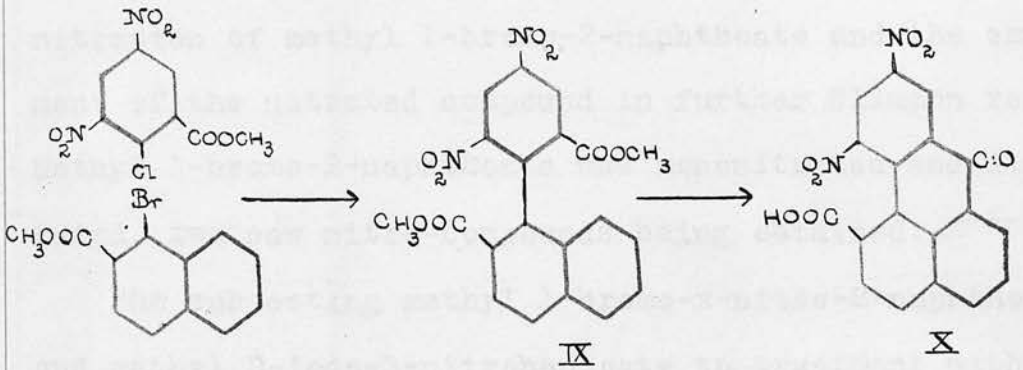
VI VII VIII

This crude product was subjected to treatment with concentrated sulphuric acid when a small amount of anthanthrone and a 52% yield of 6:6'-dinitrodiphenyl-2:2'-dicarboxylic acid were obtained. The remainder of the material, presumably the phenylnaphthyl component, appeared to be sulphonated and transformed to a water-soluble sulphonic acid.

In another experiment the same naphthalene compound was employed but methyl 2-chloro-3:5-dinitrobenzoate used

instead of methyl 2-iodo-3-nitrobenzoate in an endeavour to decrease the reactivity of the benzenoid halogen. It seemed that, in the experiment already described, the rather large yield of diphenyl dicarboxylic acid might be attributed to the relatively greater reactivity of the halogen in the benzene molecule as compared with the bromine in the naphthalene molecule.

In this second experiment it was hoped to obtain the phenylnaphthyl dicarboxylate (IX) and, from this, 9:11-dinitro-1-carboxybenzanthrone (X).

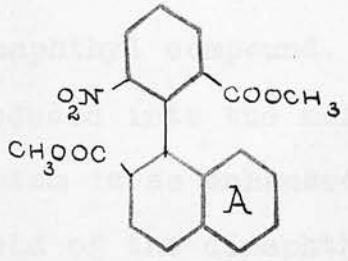


IX X

Once again it was found impossible to purify the coupling product and thus it was, as before, treated directly with concentrated sulphuric acid. A tarry material was finally obtained which could not be worked up. The presence of anthanthrone, however, was proved (green colour in sulphuric acid) and indications of sulphonation were noted.

In the two reactions described it was suspected that the required phenylnaphthyl derivative was indeed being formed but was being sulphonated in the sulphuric

acid process and lost as a water-soluble product. This sulphonation would in all probability take place in the unprotected ring A (XI below).



XI

An attempt was made to obviate this difficulty by nitration of methyl 1-bromo-2-naphthoate and the employment of the nitrated compound in further Ullmann reactions. Methyl 1-bromo-2-naphthoate was mononitrated and dinitrated, two new nitro-compounds being obtained.

On subjecting methyl 1-bromo-x-nitro-2-naphthoate and methyl 2-iodo-3-nitrobenzoate to treatment with copper bronze a 45% yield of a dinitro-dinaphthyl-dicarboxylate was obtained. No other coupled product could be detected.

An Ullmann reaction between methyl 2-iodo-3-nitrobenzoate and methyl 1-bromo-x:x_1-dinitro-2-naphthoate was productive of a 93% yield of dimethyl x:x_1:x':x_1'-tetranitro-1:1'-dinaphthyl-2:2'-dicarboxylate.

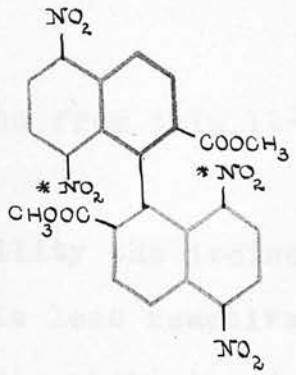
It appeared, from the results of these experiments, that the reactivity of the bromine is originally low in methyl 1-bromo-2-naphthoate and that the compound does

not react readily in the Ullmann reaction. With the introduction of a nitro-group, however, the reactivity is apparently considerably increased, causing the mono-nitro derivative to couple with itself and give a 45% yield of the dinaphthyl compound. When two nitro-groups are introduced into the molecule the reactivity of the bromine atom is so enhanced that a practically quantitative yield of the dinaphthyl dicarboxylate is obtained.

With the introduction of nitro-groups into methyl 1-bromo-2-naphthoate the capacity of the naphthalene radical to link with the benzene radical employed evidently disappears. The reactivities of the two halogen atoms are probably too widely divergent.

Dimethyl x:x'-dinitro-1:1'-dinaphthyl-2:2'-dicarboxylate was cyclised with concentrated sulphuric acid at the boiling point to yield a dinitroanthanthrone which dyed cotton from a hydrosulphite vat in fast brown shades.

Dimethyl $x:x_1:x':x_1'$-tetranitro-1:1'-dinaphthyl-2:2'-dicarboxylate gives no trace of anthanthrone formation on treatment with boiling concentrated sulphuric acid. This may be due to two of the nitro-groups being in such a position as to prevent the cyclisation.

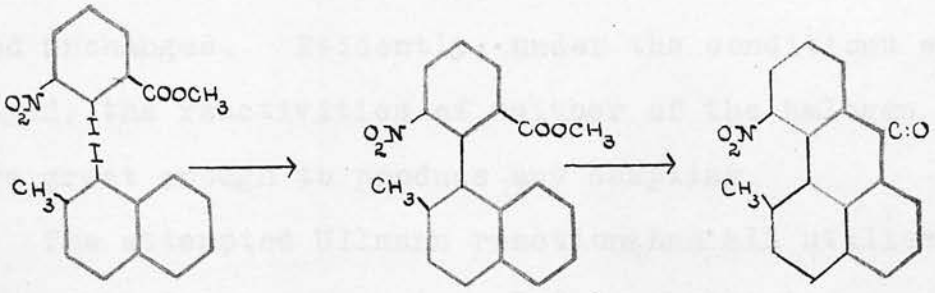


Since the nitro-compounds obtained from methyl 1-bromo-2-naphthoate did not react in the required manner in the Ullmann reaction it was considered that an attempt to orientate these derivatives would be rather superfluous. Orientation of compounds of the type of tri- and tetra-substituted naphthalenes has been shown an extremely difficult problem, constituting a research in itself. Accordingly, since the work of the present research could gain little from a knowledge of the precise nature of the methyl bromonitronaphthoates, the attempt was not made.

In another Ullmann reaction a different halogenonaphthalene derivative was substituted for methyl 1-bromo-2-naphthoate. Theoretically a 1:2-disubstituted naphthalene compound having an iodine atom in the 1-position might be suitable for use in syntheses of the required type. 1-Iodo-2-methylnaphthalene, which is not described in the literature, was synthesised from 1-amino-2-methylnaphthalene for this purpose and an attempted coupling carried out first with methyl 2-iodo-3-nitrobenzoate. It was hoped to obtain the phenylnaphthyl

derivative (XII) and, from this, 11-nitro-1-methylbenz-anthrone (XIII).

In all probability the iodine atom in 1-iodo-2-methylnaphthalene is less reactive than the bromine atom in methyl 1-bromo-2-naphthoate, due to activation of the latter by the o-substituting carbomethoxy group. On the other hand, the steric hindrance factor is probably less in 1-iodo-2-methylnaphthalene than in the bromo-naphthalene ester.

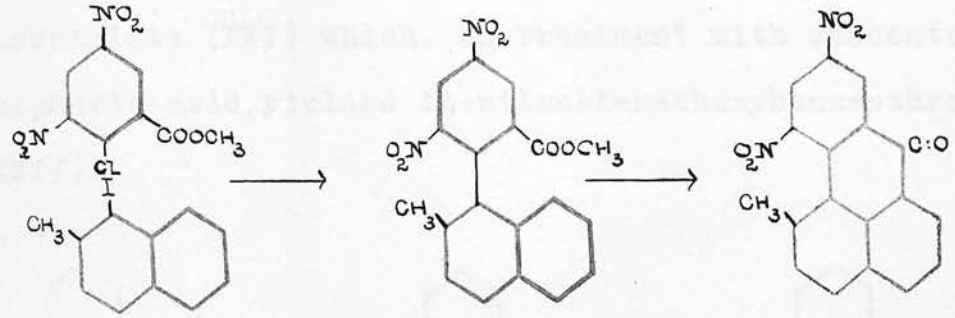


XII XIII

An 85% yield of dimethyl 6:6'-dinitrodiphenyl-2:2'-dicarboxylate was obtained from this coupling, no trace of any phenylnaphthyl or dinaphthyl derivative being detected. It appeared from this that the reactivity of the iodine atom in methyl 2-iodo-3-nitrobenzoate was considerably greater than that of the iodine atom in 1-iodo-2-methylnaphthalene.

In an endeavour to bring about an equalisation of reactivities methyl 2-chloro-3:5-dinitrobenzoate was exchanged for methyl 2-iodo-3-nitrobenzoate in another experiment. In this reaction, if successful, the

phenylnaphthyl carboxylate (XIV) and the benzanthrone (XV) should be obtained.



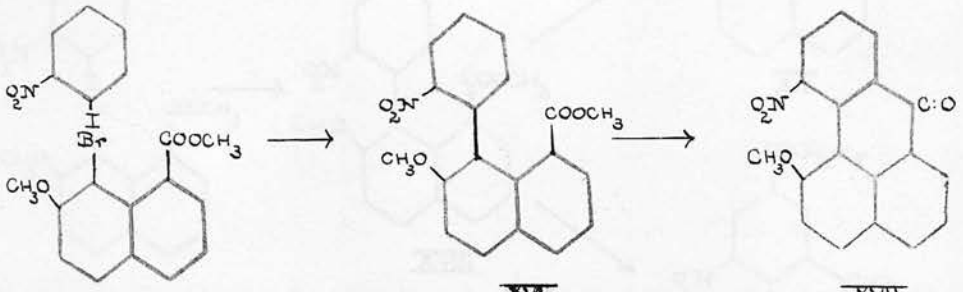
XIV XV

It was found, however, that no coupling of any nature took place, the original materials being recovered unchanged. Evidently, under the conditions employed, the reactivities of neither of the halogen atoms were great enough to produce any coupling.

The attempted Ullmann reactions had all utilised, as the naphthalene component, a 1:2-disubstituted compound. In the great majority of successful syntheses of this type, however, the esters of 8-halogeno-1-naphthoic acids have been employed. In order to synthesise a 1:11-disubstituted benzanthrone from such a compound the 7-position in the naphthalene ring must be suitably substituted. Such compounds are neither plentiful nor easy of access but one, methyl 8-bromo-7-methoxy-1-naphthoate, was prepared by J. L. Grieve (J., 1937, 537) from the corresponding acid, synthesised by Davies, Heilbron and Irving (J., 1932, 2715).

In the present work this ester and o-iodonitro-

benzene, in the presence of copper bronze under suitable conditions, gave a 51% yield of the phenylnaphthyl carboxylate (XVI) which, on treatment with concentrated sulphuric acid, yielded 11-nitro-1-methoxybenzanthrone (XVII).

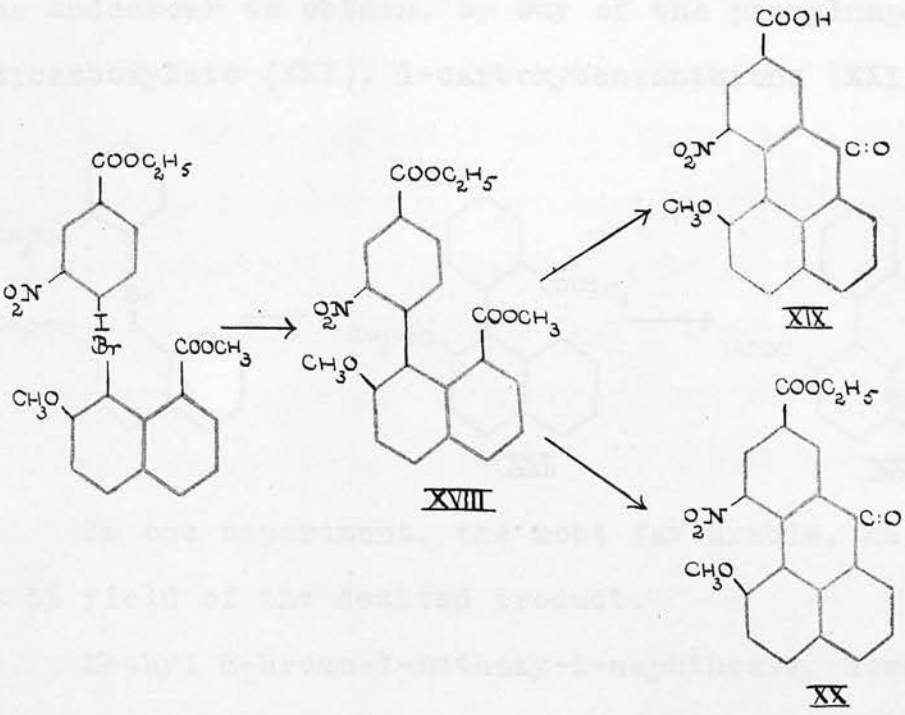


XVI XVII

In order to test further the scope of applicability of methyl 8-bromo-7-methoxy-1-naphthoate in the Ullmann reaction and, at the same time, to synthesise another 1:11-disubstituted benzanthrone which could be used to test the possibility of the existence of isomerism described later, an attempted coupling was carried out with methyl 8-bromo-7-methoxy-1-naphthoate and ethyl 4-iodo-3-nitrobenzoate. The latter ester, which is listed in the literature, but the preparation of which is not fully described, was synthesised in the present work from p-iodobenzoic acid by nitration and subsequent esterification of the nitro-iodo acid formed.

On subjecting the two above esters to the Ullmann reaction a 63% yield of the phenylnaphthyl derivative (XVIII) was obtained and, from this, by treatment with

concentrated sulphuric acid at 100°C, 11-nitro-9-carboxy-1-methoxybenzanthrone (XIX) was produced.

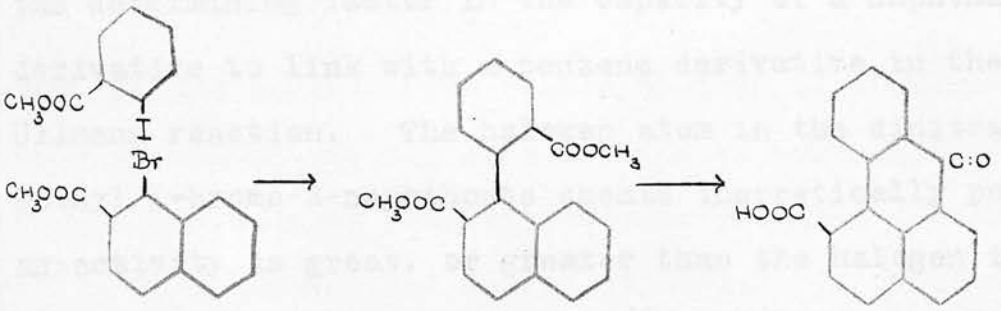


By cyclisation of (XVIII) under milder conditions (concentrated sulphuric acid at 50°C) 11-nitro-9-carboethoxy-1-methoxybenzanthrone (XX) was obtained.

The failure to obtain a phenylnaphthyl derivative when methyl 1-bromo-2-naphthoate or 1-iodo-2-methylnaphthalene was employed as one of the components in the Ullmann reaction, and the immediate success attained when methyl 8-bromo-7-methoxy-1-naphthoate was utilised in the present work seems rather surprising. What little previous work has been done with these compounds however bears out the present results.

Methyl 1-bromo-2-naphthoate and methyl o-iodobenz-

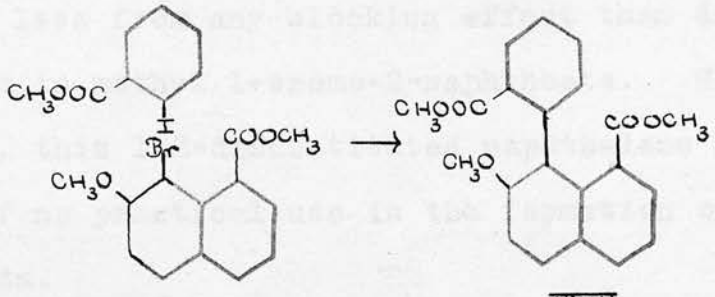
oate were treated with copper bronze under a variety of conditions by J. L. Grieve (Thesis, Edinburgh, 1936) in an endeavour to obtain, by way of the phenylnaphthyl dicarboxylate (XXI), 1-carboxybenzanthrone (XXII).



XXI XXII

In one experiment, the most favourable, he obtained a 5% yield of the desired product.

Methyl 8-bromo-7-methoxy-1-naphthoate, however, in the hands of the same worker, was coupled with methyl o-iodobenzoate to give a 52% yield of the unsymmetrical ester (XXIII).



XXIII

It thus appears that a primary factor determining the production of phenylnaphthyl derivatives of the above type rests on the 1:8-disubstituted character of the naphthalene molecule. While it has been demonstra-

ted by Rule and Barnett (J., 1932, 2728) that a carbomethoxy group in the 1-position activates an 8-substituted bromine to a great degree, it cannot be said definitely that the degree of activation of the halogen is the determining factor in the capacity of a naphthalene derivative to link with a benzene derivative in the Ullmann reaction. The halogen atom in the dinitrated methyl 1-bromo-2-naphthoate should theoretically possess an activity as great, or greater than the halogen in methyl 1-bromo-2-naphthoate or in methyl 8-bromo-7-methoxy-1-naphthoate, and yet this compound has been shown quite valueless as a starting material for the production of phenylnaphthyl derivatives by the Ullmann reaction.

In the case of 1-iodo-2-methylnaphthalene the halogen atom is not appreciably activated but apparently suffers less from any blocking effect than does the bromine atom in methyl 1-bromo-2-naphthoate. Here too, however, this 1:2-disubstituted naphthalene has been shown of no practical use in the formation of the desired compounds.

It appears that, in this field, the empirical element is still predominant and the method of trial and error the sole practicable mode of attack.

II. THE EXAMINATION OF 1:11-DISUBSTITUTED BENZANTHRONES FROM A STEREOCHEMICAL VIEWPOINT.

Chemical Examination.

It has already been stated that in 1:11-disubstituted benzanthrones the substituting groups are held in close proximity to each other, and, for this reason, it is to be presumed that a type of steric hindrance effect will arise in such compounds.

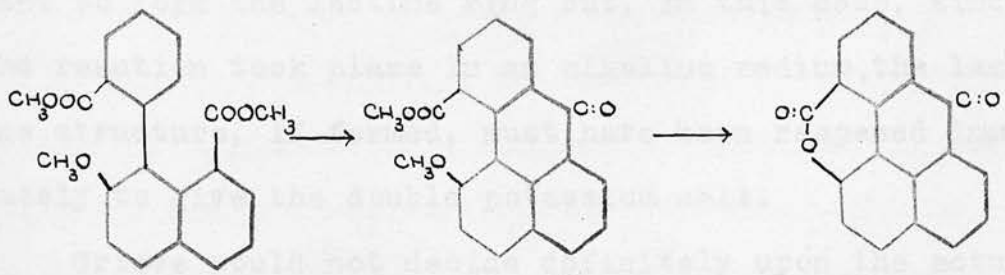
This phenomenon may be defined as one in which chemical reaction appears to be hindered or entirely suppressed by the mere presence of neighbouring atoms or groups. (Perkin and Kipping's Organic Chemistry, Part III, p. 939.)

Among the great number of examples of this effect which have been discovered and investigated perhaps the best-known occurs in the di-ortho substituted benzoic acids which are extremely difficult to esterify by the usual methods (V. Meyer and Sudborough, Ber., 1894, 27, 510, 1580, 3146). Even with only one substituent in the ortho-position, the yield of ester is substantially less than with the corresponding m- and p-acids under comparable conditions.

This being the case, a comparison of an ortho-substituted benzoic acid and a 1:11-disubstituted benz-

anthrone reveals the fact that in the latter the substituting groups are relatively much closer together than in the former. The degree of steric hindrance then should be correspondingly enhanced.

That such effects did take place was demonstrated by Grieve (loc. cit.) in an examination of methyl 7-methoxy-8-(o-carbomethoxyphenyl)-1-naphthoate (I). By analogy with the phenylnaphthyl derivative of Rule and Bigelow (J., 1935, 573) it was expected that treatment with concentrated sulphuric acid at 50°C would convert the ester into 1-methoxy-11-carbomethoxybenzanthrone (II). Such treatment, however, and even the action of concentrated sulphuric acid for a short time at room temperature, was sufficient to produce complete conversion to the lactone of 1-hydroxy-11-carboxybenzanthrone (III).

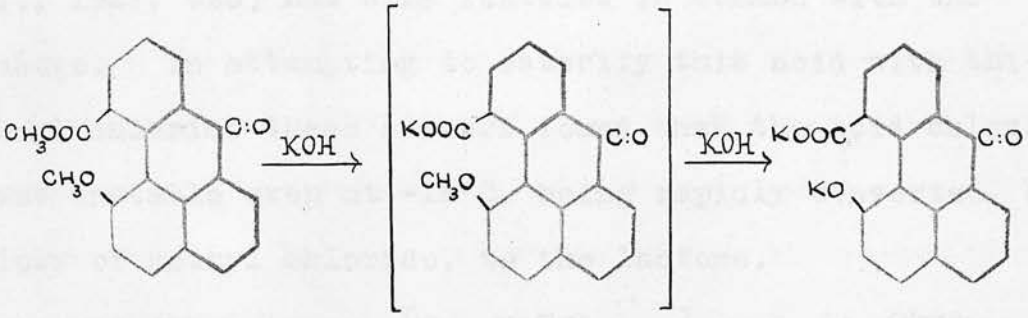


I II III

Eventually Grieve isolated the partly cyclised product by treatment of the phenylnaphthyl dicarboxylate with sulphuric acid, diluted with glacial acetic acid. Even with this reagent, however, he states that it was found difficult to arrest the course of the cyclisation, the

lactone ring being formed almost as readily as the benzanthrone structure.

By treatment of 1-methoxy-11-carbomethoxybenzanthrone with alcoholic potash Grieve also formed the lactone.



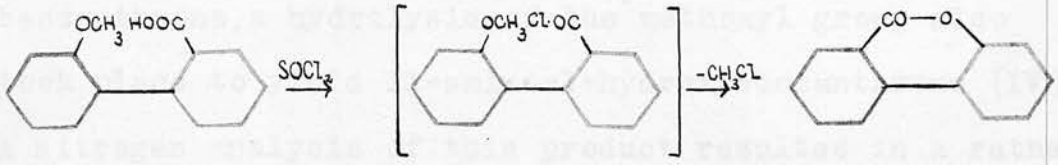
He concluded that, considering the reputed resistance of the methoxyl group to such treatment, it appeared that the intermediate methoxy acid was quite unstable under the conditions employed and that it was possible that potassium methylate was eliminated during the treatment to form the lactone ring but, in this case, since the reaction took place in an alkaline medium, the lactone structure, if formed, must have been reopened immediately to give the double potassium salt.

Grieve could not decide definitely upon the actual mechanism but attributed the abnormalities found to the possibility of formation of a stable 6-membered ring structure as is found in the lactone.

The above case forms the first example of the peculiar behaviour exhibited by a 1:11-disubstituted benz-

anthrone.

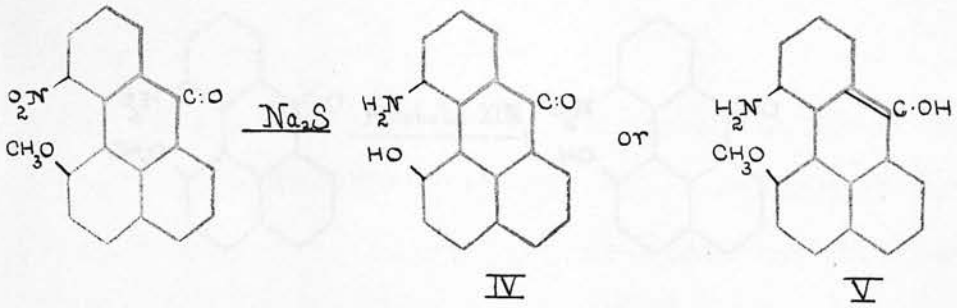
Although no exactly analogous compounds appear to have been examined previously a reaction exhibited by 2-methoxy-2'-carboxy diphenyl (Rule and Bretscher, J., 1927, 925) has some features in common with the above. In attempting to esterify this acid with thionyl chloride these authors found that the acid chloride was unstable even at -16°C, being rapidly converted, by loss of methyl chloride, to the lactone.



In the rigid benzanthrone structure the methoxyl and carboxyl groups in 1-methoxybenzanthrone-11-carboxylic acid are constantly held in close contact and, according to Grieve, it is possible that methyl alcohol may split off in a similar manner.

The examination of a compound synthesised in the course of the present work, 11-nitro-1-methoxybenzanthrone, appears to shed further light upon the above.

11-Nitro-1-methoxybenzanthrone, on being heated under reflux with aqueous sodium sulphide, went gradually into solution and an alkali-soluble aminobenzanthrone was formed. This compound was provisionally assigned one of the two possible structures (IV) or (V), the latter being of the benzanthrol type.

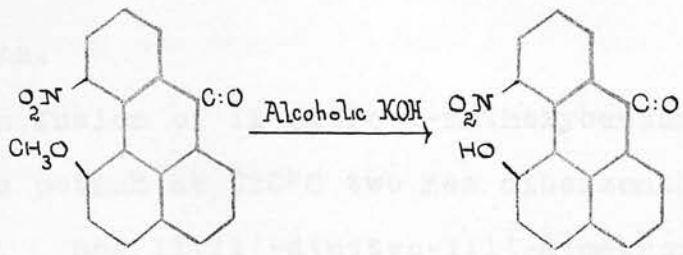


IV V

It was found, however, that benzanthrone itself, under precisely similar reducing conditions, did not exhibit any benzanthrol formation and, hence, it was presumed that, in this reduction of 11-nitro-1-methoxybenzanthrone, a hydrolysis of the methoxyl group also took place to yield 11-amino-1-hydroxybenzanthrone (IV). A nitrogen analysis of this product resulted in a rather low nitrogen figure being obtained. This will be referred to further below.

An attempted hydrolysis of 11-nitro-1-methoxybenzanthrone with dilute aqueous alkali was quite without result and thus appeared to indicate that the primary reaction in the treatment with sodium sulphide solution was a reduction of the nitro-group, followed by hydrolysis of the 11-amino-1-methoxybenzanthrone, which is apparently unstable under the conditions of experiment.

Treatment of 11-nitro-1-methoxybenzanthrone with a boiling alcoholic solution of potassium hydroxide, however, (two hours) produced almost complete conversion to an alkali-soluble product, formulated as 11-nitro-1-hydroxybenzanthrone.



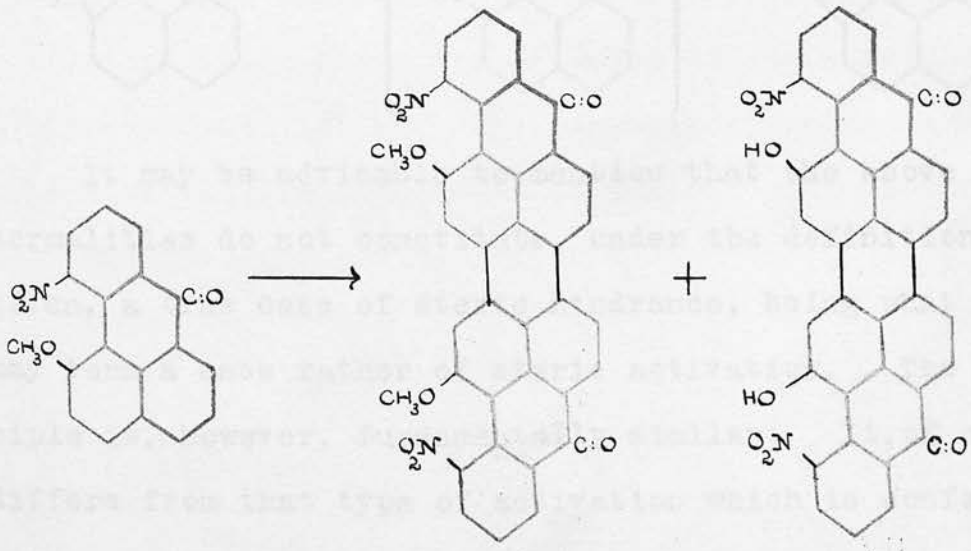
Here again, although the percentage of nitrogen found in analysis was lower than the calculated percentage, it seemed impossible to formulate for the product any other constitution than that indicated, the simple nature of the reaction and the solubility of the compound obtained in alkali, indicating that hydrolysis of the methoxyl group had indeed taken place.

Regarding the low nitrogen values recorded for these hydroxybenzanthrones it may be mentioned that the same analytical difficulty has been encountered by previous workers, Perkin (J., 1920, 698; 1922, 474) reporting that he was unable to purify 4-hydroxybenzanthrone, and quoting no melting point. More recently Boyes (Thesis, Edinburgh, 1936) attempted to synthesise 11-hydroxybenzanthrone but was unable to isolate it even in an approximately pure state.

The difficulty appears to lie chiefly in the almost complete insolubility of the majority of these compounds in almost all organic solvents, rendering it impossible to recrystallise them. Resort was made in the present work to a repeated process of boiling-out with various

solvents.

On fusion of 11-nitro-1-methoxybenzanthrone with caustic potash at 220°C two new dibenzanthrones were formed. One, 11:11'-dinitro-1:1'-dimethoxydibenzanthrone (VI), resulted from an oxidation of the benzanthrone nuclei at the positions 3 and 4 in the usual manner. The second, however, was alkali-soluble and was designated 11:11'-dinitro-1:1'-dihydroxydibenzanthrone (VII), hydrolysis of the methoxyl groups evidently taking place under the conditions employed. The latter compound was formed in much greater amount than the former. The figures given in nitrogen analyses were again rather low.

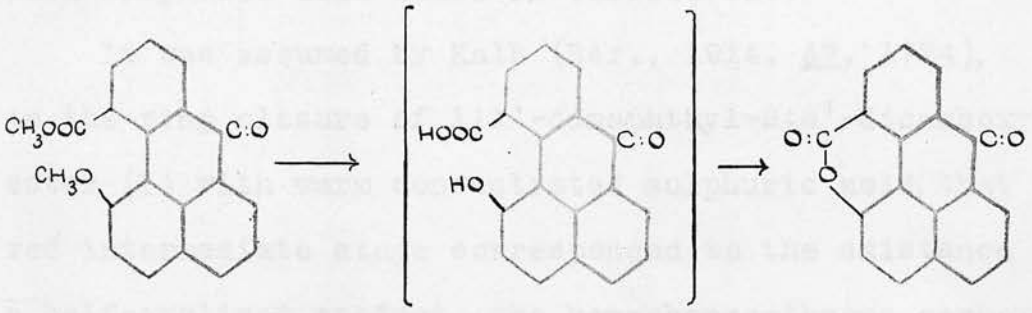


VI VII

It has thus been demonstrated in the above work that the methoxyl group in 11-nitro-1-methoxybenzanthrone is hydrolysed under conditions that normally would leave

such a group unchanged. The close proximity of the nitro-group apparently activates it in such a manner as to render it extremely labile.

It now seems reasonable to extend the above conclusion to the case of 1-methoxy-11-carbomethoxybenzanthrone and thus postulate that, in the formation of the lactone by treatment with alcoholic potassium hydroxide, a hydrolysis of both carbomethoxyl and methoxyl groups takes place, the salt of the hydroxycarboxybenzanthrone formed yielding the lactone on acidification.

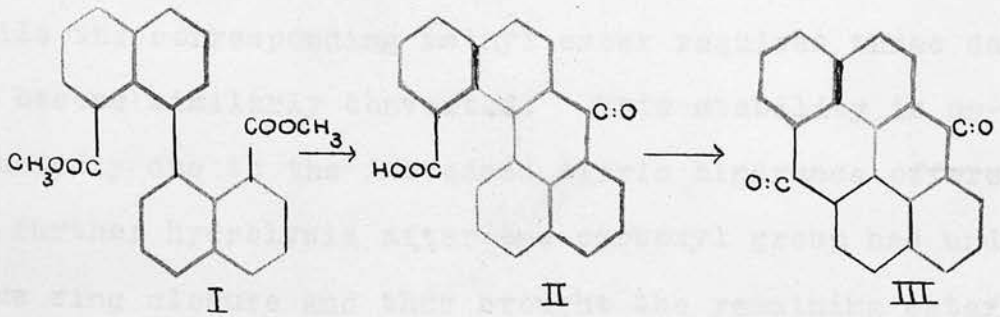


It may be advisable to mention that the above abnormalities do not constitute, under the definition given, a true case of steric hindrance, being what one may term a case rather of steric activation. The principle is, however, fundamentally similar. It, of course, differs from that type of activation which is conferred by a substituting group in a nucleus transmitting its effect through a double bond or a conjugated double bond system to the reactive group, as in, for example, o-nitrochlorobenzene which has a much more reactive halogen atom than chlorobenzene itself.

A Comparison of the Rate of Anthanthrone Formation from 10:11-Benzobenzanthrone-1'-carboxylic Acid and the Corresponding Methyl Ester on Treatment with Concentrated Sulphuric Acid.

During the present work 10:11-benzobenzanthrone-1'-carboxylic acid was prepared and a sample of the corresponding methyl ester also obtained. It was thought that an interesting comparison of the rates of anthanthrone formation from these compounds on treatment with sulphuric acid could be carried out.

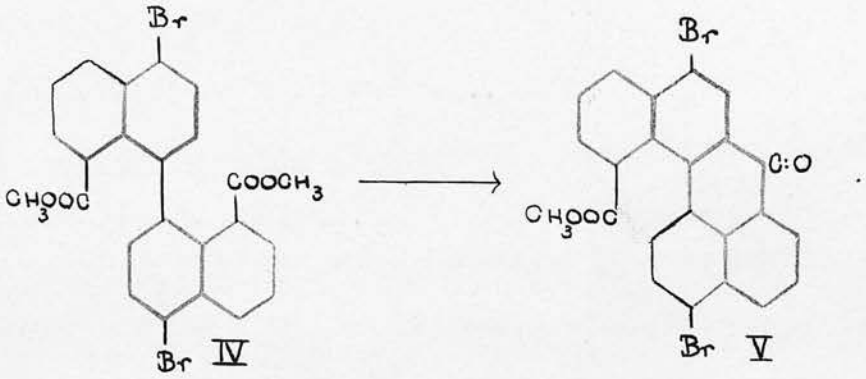
It was assumed by Kalb (Ber., 1914, 47, 1724), in the ring closure of 1:1'-dinaphthyl-8:8'-dicarboxylic ester (I) with warm concentrated sulphuric acid, that the red intermediate stage corresponded to the existence of a half-cyclised product, the benzobenzanthrone carboxylic acid (II), which underwent further ring closure to form anthanthrone (III).



I II III

Rule and Smith (J., 1937, 1099) found, however, that, if the red solution obtained by heating dimethyl

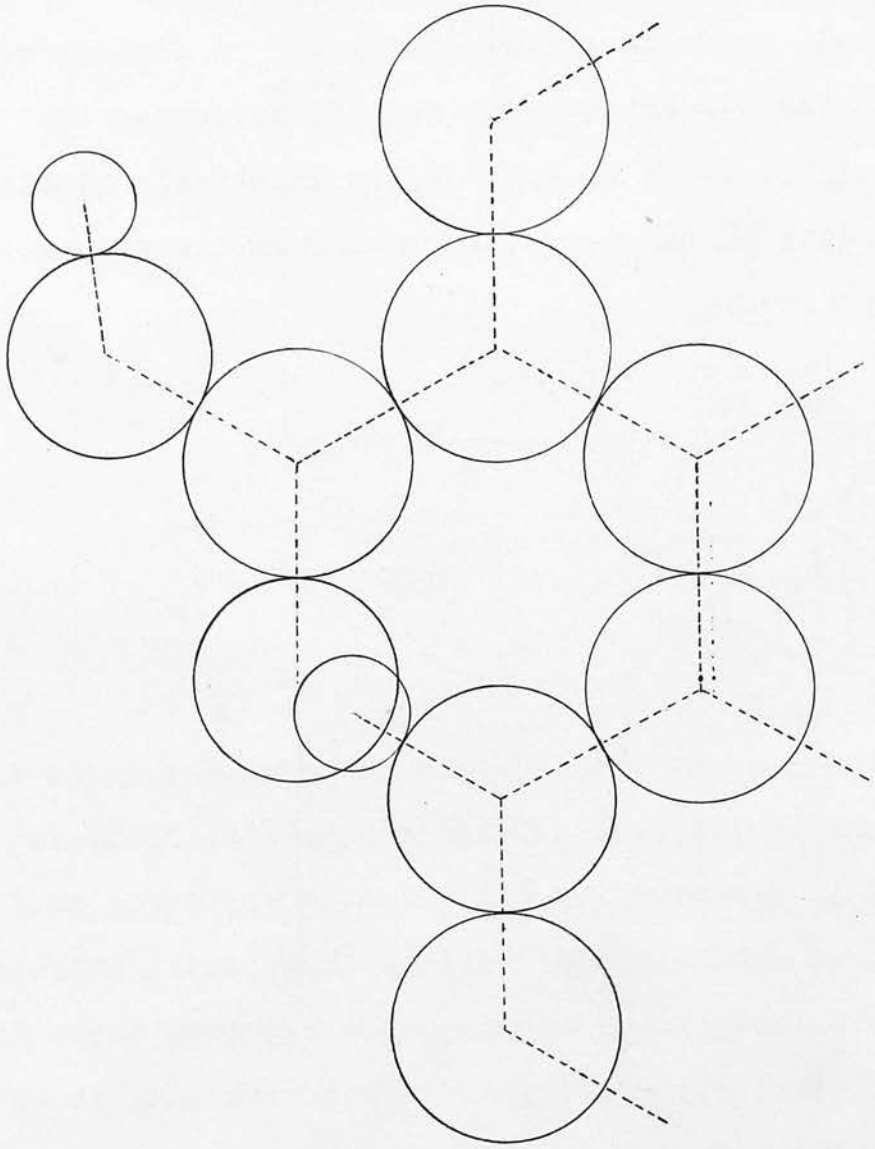
4:4'-dibromo-1:1'-dinaphthyl-8:8'-dicarboxylate (IV) with concentrated sulphuric acid was poured into water, the benzobenzanthrone carboxylic ester (V) was obtained along with some unchanged material, these latter forming the sole products of the reaction. A similar result with the unsubstituted ester (I) indicated that the monocarboxylic ester of type (V) is relatively stable under conditions which rapidly transform the free acid into anthanthrone.

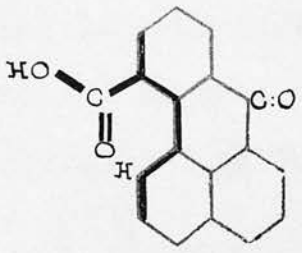


In the present research the comparison carried out has shown that 10:11-benzobenzanthrone-1'-carboxylic acid (II) is converted by concentrated sulphuric acid at 50°C into anthanthrone (III) in about thirty minutes while the corresponding methyl ester requires three days to become similarly converted. This stability is undoubtedly due to the increased steric hindrance offered to further hydrolysis after one carboxyl group has undergone ring closure and thus brought the remaining ester grouping into the same plane as the benzanthrone molecule in spatial proximity to the 1-position. In the related

SCALE DIAGRAM OF PART OF THE 11-CARBOXYBENZANTHRONE MOLECULE.

The formula at the extreme bottom forms a key to the scale diagram.





free acid the carboxyl group is held rigorously in the most favourable position for rapid conversion to anthanthrone. Kalb (loc. cit.) has thus been shown incorrect in his assumption, it being demonstrated that the intermediate present in the red solution obtained by treating the dinaphthyl dicarboxylic ester with sulphuric acid is predominantly the methyl benzobenzanthrone carboxylate and not the acid to which it gives rise on hydrolysis.

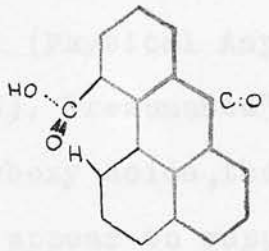
Optical Examination.

The reactions of 1-methoxy-11-carbomethoxybenzanthrone and of 11-nitro-1-methoxybenzanthrone have, in the above, been attributed to the close spatial proximity of the 1:11-substituting groups. In the scale diagram opposite, drawn according to atomic radii quoted by Boyes (Proc. Roy. Soc., 1934, 144, 683), and representing part of the carboxybenzanthrone molecule, the proximity of the two positions is emphasised.

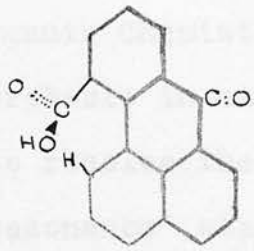
This diagram, however, suggests a further consequence of the spatial configuration, namely a considerable restriction of the rotation of the carboxyl group around the bond joining it to the nucleus, by the blocking effect of the hydrogen atom in the 1-position. This restriction indeed appears to be greater than in the

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case of many resolvable diphenyls. It seems therefore that the existence of two stereoisomeric forms of 11-carboxybenzanthrone might be possible. The two possible enantiomorphs are represented diagrammatically in (I) and (II), the ketonic oxygen being above the plane of the paper in the former and lying below in the latter.



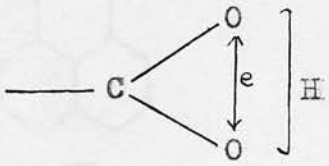
I



II

This consideration led to an attempt by J. L. Grieve (Thesis, Edinburgh, 1936) to resolve the acid. He found, however, that neither the brucine salt nor the *l*-menthyl ester could be separated into fractions having different rotations, nor did the brucine salt exhibit any mutarotation in pyridine solution. The examination therefore gave no indication of the existence of stereoisomeric forms of 11-carboxybenzanthrone.

In an endeavour to explain the non-resolvability of the above compounds Grieve took refuge in the recent suggestion that the carboxyl group, in the free state at least, is symmetrical, involving an electrical "resonance" state which may be represented as follows.

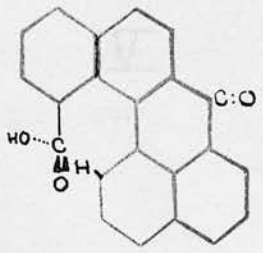


If this is the case the existence of stereoisomeric forms of 11-carboxybenzanthrone obviously becomes impossible. Moreover, if the free acid possesses this "resonance" structure, a similar structure will almost certainly be present in the brucine salt where similar electrovalent linkages are present.

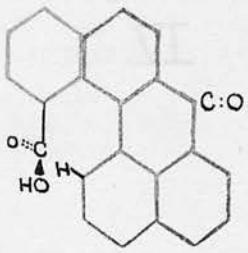
Grieve further states that since, according to Waters (Physical Aspects of Organic Chemistry, Routledge, p. 396), "resonance" is also probable in esters and amides of carboxy acids, the failure to resolve the menthyl ester would appear to support the "resonance" state.

In the present work a sample of the *l*-menthyl ester of 11-carboxybenzanthrone prepared by Grieve was examined for mutarotation in pyridine solution. It failed to exhibit any effect and thus completed the above findings.

Before an attempt was made to obviate the "resonance" difficulty described, another closely related compound was prepared in which the carboxyl group approaches even more closely to the nuclear hydrogen than is the case in 11-carboxybenzanthrone. This compound, 10:11-benzobenzanthrone-1'-carboxylic acid, may exist in the two stereoisomeric forms (III) and (IV).



III

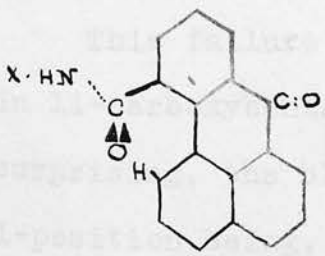


IV

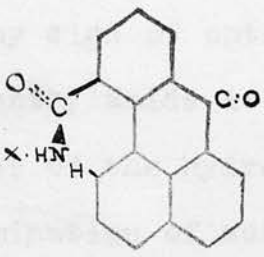
The cinchonine salt of this acid was prepared and repeatedly recrystallised. No change in rotation, however, was detected, nor did a sample of the final product exhibit mutarotation when dissolved in pyridine. It may be mentioned that considerable difficulty was found in forming an alkaloidal salt of the benzobenzanthrone carboxylic acid due, possibly, to a steric hindrance effect (See Experimental Section).

So far, then, the results of the present work appeared to support the work of Grieve and the "resonance" theory, the symmetry of the "resonant" carboxyl group rendering any attempt at resolution abortive.

It was seen, however, that even if this "resonance" state extended to the amides and substituted amides of carboxylic acids, a dissymmetrical structure would still exist in the latter and they should be capable of resolution into the stereoisomerides represented below, V and VI.

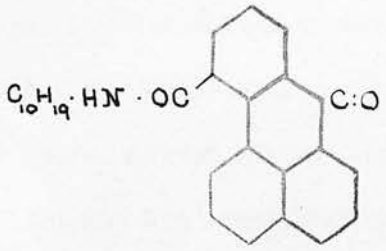


V



VI

To put this theory to a test the acid chloride of 11-carboxybenzanthrone was treated with ℓ-menthylamine and 11-carboxybenzanthrone-ℓ-menthylamide (VII) prepared.



VII

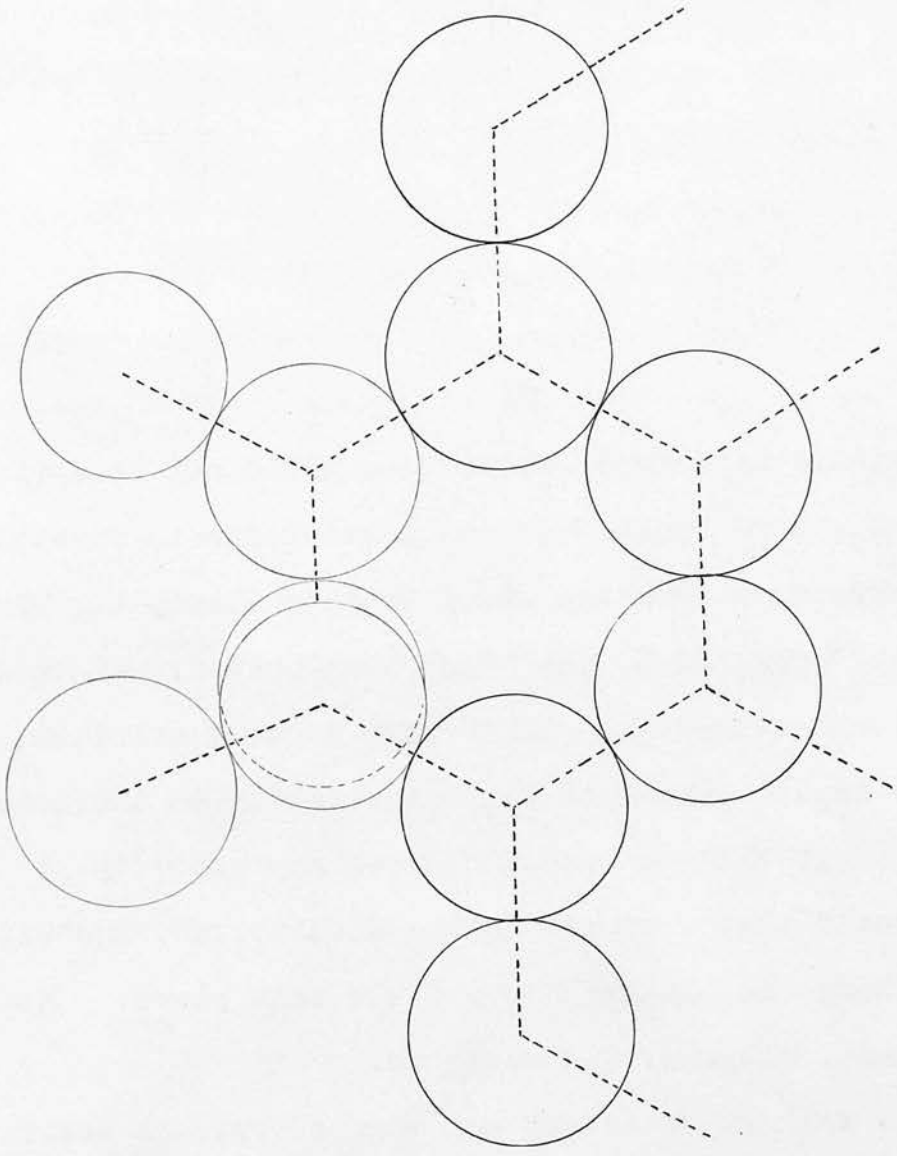
Ordinary methods of resolution could not be applied to this compound because of its unreadiness to crystallise in pure form from the usual organic solvents. The substance, purified by the adsorption method, was therefore allowed to deposit slowly from benzene solution, and this deposit examined for mutarotation in the same solvent. If the compound possessed any activity it was expected that a change in the equilibrium, and with this, a change in the rotation, would take place. No such change, however, was observed.

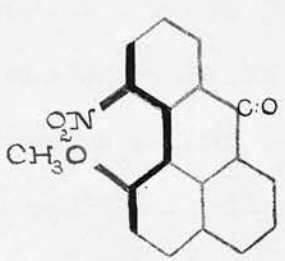
This failure to detect any sign of optical activity in 11-carboxybenzanthrone-ℓ-menthylamide is somewhat surprising, the blocking effect of the hydrogen in the 1-position being, from an examination of scale models, definitely present. If this compound is indeed non-resolvable it can be argued that the non-resolvability

SCALE DIAGRAM OF PART OF THE

11-NITRO-1-METHOXYBENZANTHRONE MOLECULE.

The hydrogen atoms are omitted in this representation. The formula at the extreme bottom forms a key to the scale diagram.



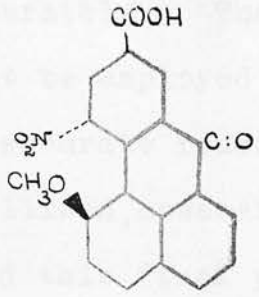


of the brucine salt and ℓ-menthyl ester of 11-carboxybenzanthrone; of the cinchonine salt of 10:11-benzobenzanthrone-1'-carboxylic acid cannot be explained solely on the basis of a resonance structure, some other condition being present in all these compounds which militates against the existence of enantiomorphic forms. It must be admitted, however, that negative results in work of this nature can never be conclusive and that in the case of 11-carboxybenzanthrone-ℓ-menthylamide the evidence is too scanty to give any definite answer to the resonance problem. This will be further referred to below.

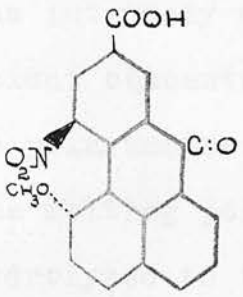
In the 11-nitro-9-carboxy-1-methoxybenzanthrone molecule the question of possibility of existence of optical isomerides also appears to arise. This possibility, although depending too on the close spatial proximity of the 1:11-substituting groups, yet differs from the examples already cited.

The two groups, as shown in the diagram opposite, do not appear to have space in which to assume their normal positions and thus will presumably be deviated from these positions in the cyclisation of the parent phenylnaphthyl derivative to the benzanthrone. In the latter they may be assumed to lie side by side, the bonds joining them to the nuclear carbon atoms being inclined at an angle to the plane of the benzanthrone

molecule. The two possible enantiomorphs are represented in (VIII) and (IX).



VIII



IX

The cinchonine salt of 11-nitro-9-carboxy-1-methoxybenzanthrone was first prepared and crystallised repeatedly. A change in specific rotation of 27° (λ 6300 Å) was observed between the rotations of initial and final product (+136° — +109°), this change also being parallelled by an initial decrease in the melting point of the salt followed by a subsequent rise to a steady value. It thus appeared that some resolution was being effected. A sample of the final product, on hydrolysis to the parent acid, however, exhibited no activity in alkaline solution, nor did another sample give any detectable mutarotation in pyridine.

Before any conclusions were drawn regarding the somewhat anomalous results obtained with the cinchonine salt it was decided to prepare another alkaloidal salt of the same benzanthrone carboxylic acid and carry out a similar examination. The strychnine salt was prepared for this purpose.

This strychnine salt crystallised in three fractions from the reaction mixture and these fractions were examined separately. The first was intensely coloured and could not be employed in sufficient concentration to give an accurate reading in the polarimeter. It was recrystallised, however, until the melting point became fixed and this final product hydrolysed to the free acid. The latter gave no rotation in alkaline solution.

The second fraction, with an initial specific rotation of +14·3°, on one recrystallisation yielded a product of specific rotation +7·1°.

The third fraction possessed a specific rotation of +6·6°. On mixing the recrystallised second fraction with the third fraction and a further recrystallisation of this composite a sample of the strychnine salt of specific rotation +7·0° was obtained (all rotations at λ 6300 Å).

Hydrolysis of this final product yielded the free acid which again exhibited no activity in alkaline solution; nor did a sample of the recrystallised salt show any mutarotation in pyridine.

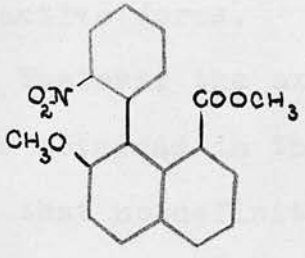
Before discussing these results it may be mentioned that the intensity of colour possessed by the strychnine salt and, to a lesser extent, the cinchonine salt, made it necessary to employ rather low concentrations in the preparation of solutions for optical examination. The

experimental error was thus rather higher than usual in this type of work but never exceeded 3%.

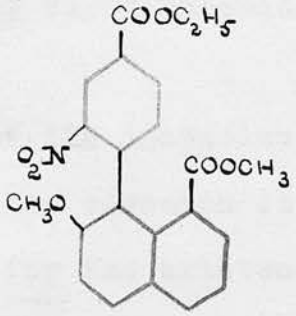
The relative insolubility of the acid itself rendered it necessary to examine it for optical activity in the form of its sodium salt.

The results obtained above appeared to indicate that a resolution of the alkaloidal salts of 11-nitro-9-carboxy-1-methoxybenzanthrone was being affected on recrystallisation although the failure to obtain an active acid from the presumably active salts, and the absence of any mutarotation effect in these salts, seems rather difficult of explanation. It may be, however, that the active forms of the benzanthrone carboxylic acid are unstable and suffer extremely rapid racemisation in alkali, the same applying to the alkaloidal salts in pyridine solution.

A further point which appears to have some bearing on this question is the ease with which the phenyl-naphthyl derivatives (X) and (XI) cyclise to the corresponding benzanthrones on treatment with concentrated sulphuric acid.

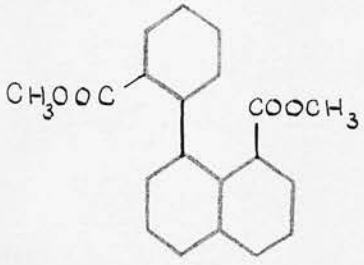


X

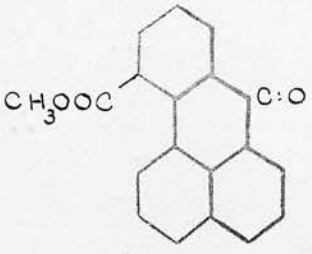


XI

Heating at 50°C for fifteen minutes with sulphuric acid was sufficient to cyclise completely either of these derivatives. This is relatively mild treatment in work of this kind, it having been found, for example, that to obtain 11-carbomethoxybenzanthrone (XIII) from the corresponding phenylnaphthyl derivative (XII), one hour's treatment with concentrated sulphuric acid at 50°C is necessary.



XII



XIII

It thus appears from the above that the 1:11-di-substituting groups in question have no blocking effect as far as cyclisation is concerned. It may even be asked whether these groups, despite the inferences drawn from the atomic scale diagrams, may not be either superimposed upon one another in such a manner as to form a symmetrical structure, or capable of free passage past one another so as to bring about rapid racemisation of the active forms.

Whatever the explanation of the inconclusive results obtained in this part of the research it may be said that no definite evidence for the existence of

enantiomorphic forms of 11-carboxybenzanthrone, 10:11-benzobenzanthrone-1'-carboxylic acid or of 11-nitro-9-carboxy-1-methoxybenzanthrone has been obtained. Indeed the cumulative results seem to point to the conclusion that such types of activity are non-existent under the conditions employed.

III CHROMATOGRAPHIC ADSORPTION.

Practical advances in biochemistry and organic chemistry not infrequently owe their origin to the extension of physico-chemical technique into their spheres. One of such advances is that now termed chromatographic adsorption or, shortly, chromatography.

If a homogeneous solution of several strongly-coloured compounds is shaken with a suitable adsorbent it is found that a partition takes place between the two phases, the degree of partition depending upon the individual concentrations of the components of the solution and their relative adsorption coefficients. The components will thus be adsorbed on the adsorbent in varying degrees. The adsorbate will not be, as a rule, of the same composition as the original dissolved mixture, and a partial separation will have been effected. This separation, though real, is yet crude and of little practical utility.

The extension, however, of this fundamental property is productive of important developments and consists in the passage of the coloured solution over the adsorbent in one definite direction.

Tswett in 1906 passed a petroleum ether extract of green leaves down a vertical glass tube packed with powdered calcium carbonate and found that the apparently

homogeneous pigment showly separated into adsorption bands upon the adsorbent. On the upper part of the tube a yellow band formed; below that two distinct green bands and, lower, three yellow bands made their appearance. On pouring pure solvent down the tube the bands formed in the initial adsorption process were spread and spaced further apart, or "developed" to constitute the "chromatogram".

The next stage consisted in cutting the tube into sections indicated by the bands, treating each section with a suitable solvent, and filtering off the adsorbent. The solutions so obtained could then be examined chemically or spectroscopically.

By this investigation Tswett proved the composite nature of chlorophyll and of the leaf-yellows. Further, he had given birth to a new technique of wide applicability and far-reaching possibilities.

A simple chromatographic experiment consists accordingly of the following operations:

the preparation of the adsorption tube;
the passage of the solution to be investigated;
the development of the primary adsorbate by the passage of pure solvent;
the division of adsorbent with its adsorbate into sections, as indicated by the bands formed;

the elution of the individual sections;
the separation of eluted material from adsorbent, and
the working up of the final solutions obtained.

Although this technique admits of modification to meet the exigencies of individual cases the general scheme remains broadly unaltered.

In 1910 Tswett published the results of his work in "Chromofilli w Rastitelnom i Schivotnom Mirje" but this, due mainly to its being written in the Russian language, lay practically unnoticed for over two decades.

The years 1906 to 1931 may be termed a latent period in chromatographic adsorption work. In sharp contrast to this sterile phase, however, recent years have been marked by surprising developments in the subject. Among its many successful applications may be mentioned the separation of the carotinoids by Kuhn and Lederer; of the flavines by Karrer, Koschara, Kuhn; and of some water-soluble coal-tar dyestuffs by Ruggli and Jenson. Problems of purification and separation in many fields have been attacked by the new technique and, if success has not been invariably attendant, it can be said that the adsorption method places yet another weapon in the armoury of the organic chemist; gives to him a tool at once delicate, flexible, adaptable, the value of which cannot as yet be fully assessed.

The theory underlying the adsorption of materials from solution in well-defined bands on the adsorbent is superficially simple. The primary process consists in a general and rather poorly-differentiated adsorption. On the passage of pure solvent, however, over the adsorbate an equilibrium tends to be set up between the components of the adsorbate and the solvent. The more weakly adsorbed substances will pass, to a greater or less extent, into solution, will be carried a little way down the tube, and be readsorbed. The continuous repetition of this process will thus, in the ideal case, produce complete separation.

The materials employed in this work are many and varied. Generally speaking, almost any solid substance can be utilised as an adsorbent. Among these may be mentioned aluminium oxide, calcium carbonate, calcium hydroxide, magnesium hydroxide, quartz, lactose, etc.

The choice of solvent to be used in adsorption work is, of course, largely determined by the nature of the material it is proposed to examine. Petroleum ether (b.p. not over 80°C) is probably the most frequently used solvent; benzene, carbon disulphide, chloroform, carbon tetrachloride, dichloromethane and ether, in roughly the order given, are also useful. Mixtures of solvents are frequently utilised.

Alcohol, acetone, and ether fulfil the role of

eluting agents in the majority of cases.

In dealing with colourless substances many expedients have been resorted to. Perhaps the most valuable is the exploitation of the capacity of fluorescence exhibited by most aromatic compounds under ultra-violet light, the adsorption tube being examined from time to time under irradiation as the process proceeds. The bands formed then fluoresce in a variety of colours and shades, their position in the tube is marked, and the tube cut as indicated.

The first occasion on which chromatographic adsorption methods were utilised in the present research was in the purification of 11-carboxybenzanthrone-ℓ-menthylamide. This compound, prepared from the acid chloride of 11-carboxybenzanthrone and ℓ-menthylamine, could not be recrystallised successfully, being deposited from petroleum ether-benzene mixtures in the same crude state as the original material. Attempts to recrystallise the substance from other solvents were all productive of similar results. The examination of 11-carboxybenzanthrone-ℓ-menthylamide for possible optical activity, however, demanded that purification be effected.

The problem was ultimately solved quickly and efficiently by the selective adsorption of the substance on anhydrous aluminium oxide from benzene solution. By this process the crude material was separated on the

oxide into three bands, a visible yellow band containing the pure amide, and two other bands, visible only under ultra-violet irradiation, and due to the presence of small amounts of impurities. The pure amide was obtained from the yellow band in 70% yield, the melting point being raised, in one operation, from 195°-202°C (with previous sintering and partial melting at 79°-100°C) to 214°-216°C (with previous sintering over the range 98°-103°C).

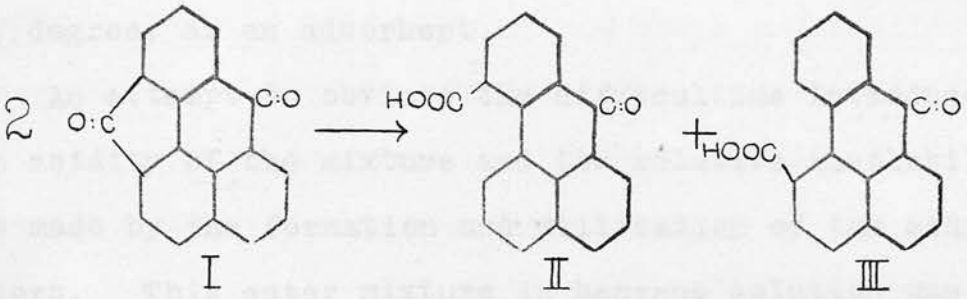
A further adsorption of the purified product gave no elevation of the melting point. This fact, coupled with the results of analysis, was deemed sufficient to indicate that the limits of purification had been attained immediately.

The definite sintering reported above appears to be, on the evidence available, an intrinsic property of amides and substituted amides of benzanthrone carboxylic acids, Boyes (Thesis, Edinburgh, 1936) having shown that the amide of 11-carboxybenzanthrone exhibits a definite sintering range. Many other derivatives of this type behave in the same manner.

The successful separation of 11-carboxybenzanthrone-*l*-menthylamide from attendant impurities by the adsorption method led to an attempt being made to separate, by a similar technique, the mixture of 1-carboxybenzanthrone and 11-carboxybenzanthrone obtained by the alkaline hyd-

rolysis of 1:11-ketobenzanthrone.

Rule and Bigelow (J., 1935, 573) observed that 1:11-ketobenzanthrone (I), on prolonged heating with aqueous alkali, suffers rupture at the ketonic link to produce, presumably, a mixture of acids consisting of 11-carboxybenzanthrone (II) and 1-carboxybenzanthrone (III).



I II III

Rule and Bigelow (unpublished) carried out an examination of this acid mixture in an attempt to isolate 1-carboxybenzanthrone and showed that repeated recrystallisation of the acids or their metallic salts resulted in a concentration of 11-carboxybenzanthrone and eventually led to the isolation of extremely small amounts of that isomeride in the pure state.

Grieve (Thesis, Edinburgh, 1936) resumed this work and endeavoured to obtain the 1-carboxylic acid by partial esterification and also by partial acidification of an alkaline solution of the mixture. These resorts failed to effect any apparent separation of the isomers. Nor did the fractional distillation of the mixed methyl esters (obtained by esterification of the acids) appear

to bring about a concentration of either derivative.

In the present work, using the adsorption method, it was found that no separation of the acid mixture could be effected using, as adsorbents, aluminium oxide or lactose, the oxide presumably forming aluminium salts with the substance in acetone solution due to traces of water being present, and the lactose failing to act, in any degree, as an adsorbent.

An attempt to obviate the difficulties introduced by the acidity of the mixture and its relative insolubility was made by the formation and utilisation of the ethyl esters. This ester mixture, in benzene solution, was passed over aluminium oxide when undifferentiated adsorption took place. The band formed was washed with benzene, was greatly extended, and was cut into two portions; the process was then repeated on each portion. By repetition of this method and subsequent recrystallisation (twice) of one of the final fractions a 15% yield of pure ethyl benzanthrone-11-carboxylate was obtained. No isolation of ethyl benzanthrone-1-carboxylate was effected, but as the process proceeded, it seemed that the proportion of this isomeride in the mixture must be relatively small.

An interesting feature of this attempted separation was the production of one of the pure components of the mixture in quotable yield. Rule and Bigelow did not

succeed in obtaining appreciable quantities of 11-carboxybenzanthrone in their tedious separation by fractional crystallisation.

Two further purifications of substances by adsorption methods were also successfully carried out in the present work, dimethyl x:x'-dinitro-1:1'-dinaphthyl-2:2'-dicarboxylate and dimethyl $x:x_1:x':x_1'$-tetranitro-1:1'-dinaphthyl-2:2'-dicarboxylate being satisfactorily recrystallised only after a preliminary adsorption from acetone solution on aluminium oxide when small amounts of a dark-coloured impurity were retained by the adsorbent.

The difficulty of obtaining hydroxybenzanthrones in the pure state met with during the present work and commented upon by previous workers in the same field led inevitably to thoughts of purification of these compounds by the above methods. The extremely sparing solubility of these substances, however, in almost all organic solvents forms an insuperable bar to the successful utilisation of adsorption technique.

To sum up, the use of chromatographic adsorption methods in the present work has been productive of satisfactory results. 11-Carboxybenzanthrone-ℓ-menthylamide has been purified by adsorption where the normal methods failed; ethyl benzanthrone-11-carboxylate has been isolated for the first time in quotable yield from the

esterified mixture produced in the alkaline hydrolysis of 1:11-ketobenzanthrone; and two further new compounds have been obtained in the pure state with greater facility than would otherwise have been the case.

EXPERIMENTAL SECTION

The experimental work carried out is described in the following pages. Yields of products are quoted as percentages of the maximum theoretical amounts obtainable. Melting points are corrected, the thermometer used having been calibrated against short-stemmed "standard thermometers". All new compounds have been analysed by Dr Weiler (Oxford), Dr Schoeller (Berlin), or in the Department of Medical Chemistry in the University of Edinburgh by Mr Brown, lecture assistant.

Preparations described in the literature, and which have been repeated in the course of this work without modification, are not described fully, references, yields and melting points only being given.

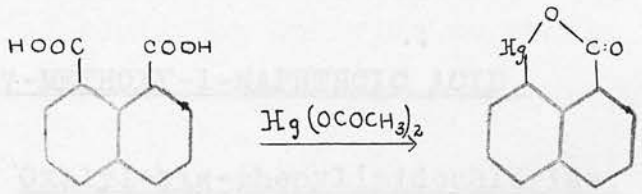
Preparations carried out without modification, modified preparative methods, and syntheses of new compounds are designated as such in the index of preparations.

PREPARATIONS

8-BROMO-1-NAPHTHOIC ACID.

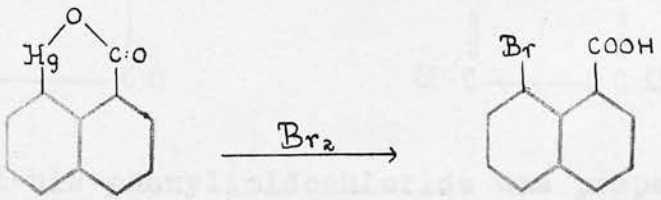
This preparation was carried out by the method of Rule and co-workers (J.C.S., 1934, 170).

a) Mercuration of naphthalic acid.



From 54 gm. naphthalic acid a 97% yield of the mercury compound was obtained.

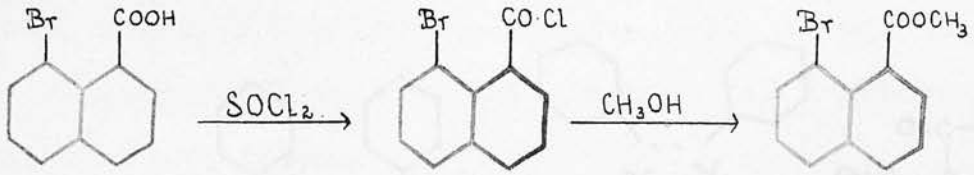
b) Bromination of the mercury compound.



Anhydro-8-hydroxymercuri-1-naphthoic acid (80 gm.) gave 33 gm. of the pure bromo-acid after recrystallisation from benzene.

Yield: 57%. M.p. 178°C.

Methyl 8-bromo-1-naphthoate.

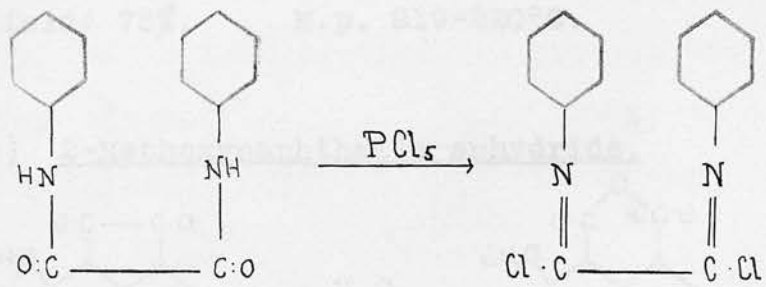


The esterification of 8-bromo-1-naphthoic acid was carried out according to the method of Rule and Barnett (J.C.S., 1932, 175). From 15 gm. acid 15 gm. ester was obtained, corresponding to a yield of 95%.

M.p. 31-32°C.

8-BROMO-7-METHOXY-1-NAPHTHOIC ACID.

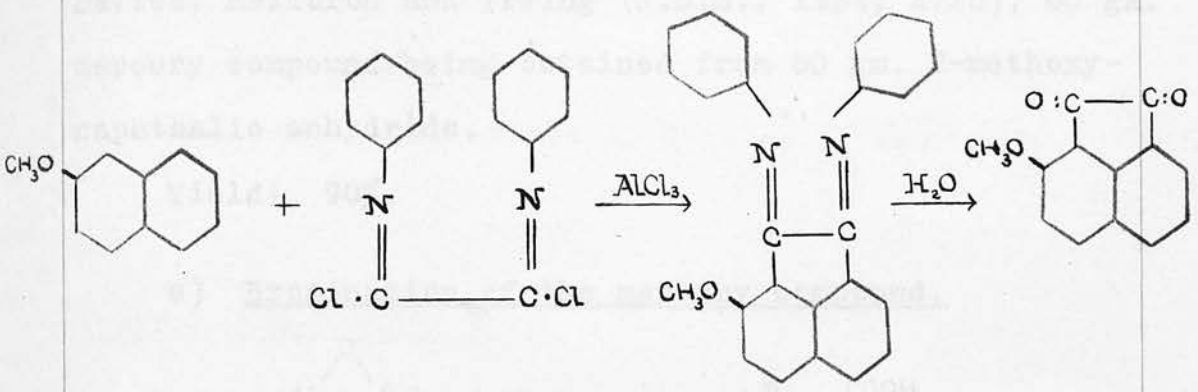
a) Oxalyl-bis-phenylimidochloride.



Oxalyl-bis-phenylimidochloride was prepared by the method of Bauer (Ber., 1907, 40, 2650), 45 gm. being the yield from 50 gm. oxanilide (80%).

M.p. 113-114°C.

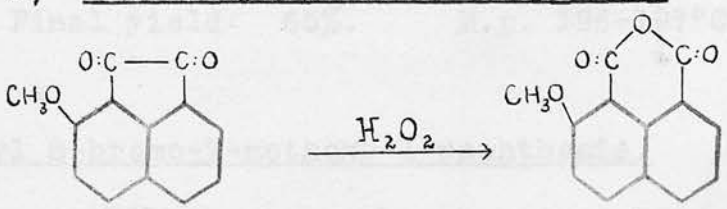
b) 2-Methoxyacenaphthenequinone.



Oxalyl-bis-phenylimidochloride (82·2 gm.) and β-naphthyl methyl ether (90 gm.) were condensed in the presence of aluminium chloride according to the method of Staudinger, Goldstein and Schlenker (Helv. Chim. Acta., 1921, 4, 342), and the condensation product hydrolysed to give 45 gm. of the methoxy-quinone.

Yield: 75%. M.p. 219-220°C.

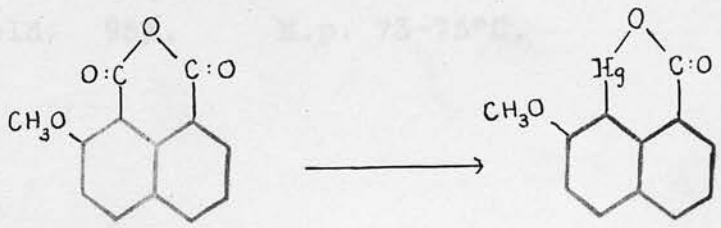
c) 2-Methoxynaphthalic anhydride.



The oxidation method of Whiston (J. Soc. Chem. Ind., 1924, 43, 370), employing hydrogen peroxide, gave 26·5 gm. anhydride from 25 gm. quinone.

Yield: 90 - 95%. M.p. 259°C.

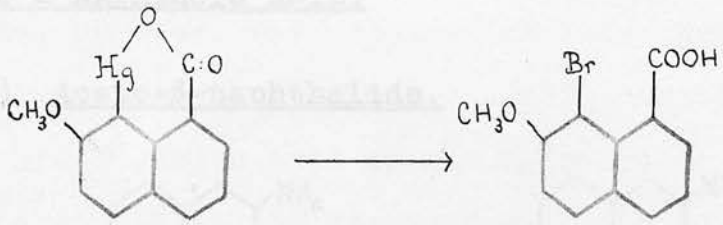
d) Mercuration of the anhydride.



The anhydride was mercurated as described by Davies, Heilbron and Irving (J.C.S., 1932, 2715), 80 gm. mercury compound being obtained from 50 gm. 2-methoxy-naphthalic anhydride.

Yield: 90%.

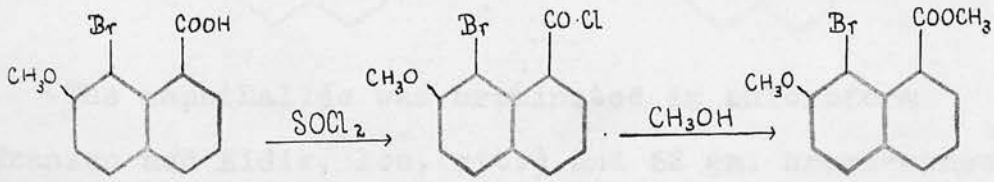
e) Bromination of the mercury compound.



The mercury compound was brominated in boiling glacial acetic acid solution (Davies, Heilbron and Irving, loc. cit.), 14 gm. pure 8-bromo-7-methoxy-1-naphthalic acid being prepared from 30 gm. mercury compound. The initial bromination product was recrystallised from alcohol.

Final yield: 65%. M.p. 196-197°C.

Methyl 8-bromo-7-methoxy-1-naphthoate.



The ester was prepared according to the method of J. L. Grieve (Thesis, Edinburgh, 1936).

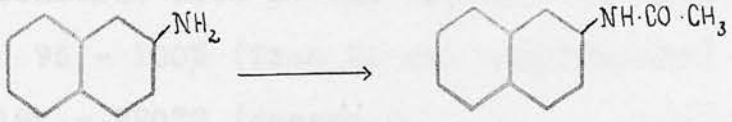
Yield: 95%. M.p. 73-75°C.

On recrystallisation from petroleum ether (b.p. 60° - 80°C) stout colourless needles of melting point 79°C were obtained.

(Melting point quoted by Grieve, 79°C.)

1-BROMO-2-NAPHTHOIC ACID.

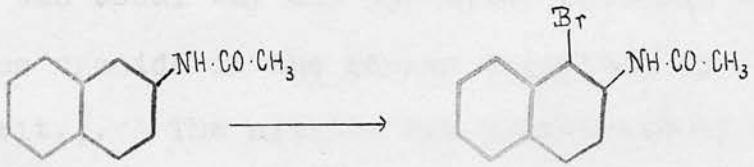
a) Aceto-β-naphthalide.



β-Naphthylamine (100 gm.), on acetylation with acetic anhydride according to the method of Franzen and Eidis (J. pr. Chem., 1913, 88, 755), gave 120 gm. acetyl compound.

Yield: 95 - 100%. M.p. 133°C.

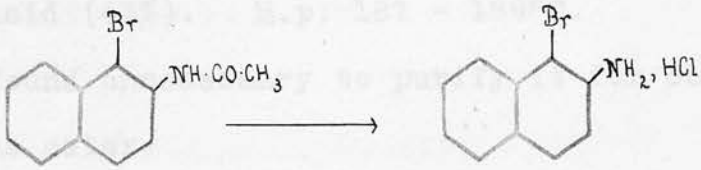
b) Aceto-1-bromo-2-naphthalide.



The naphthalide was brominated in chloroform (Franzen and Eidis, loc. cit.) and 52 gm. bromo-compound obtained from 37 gm. aceto-β-naphthalide.

Yield: 95 - 100%. M.p. 138°C.

c) Hydrolysis of the bromonaphthalide.

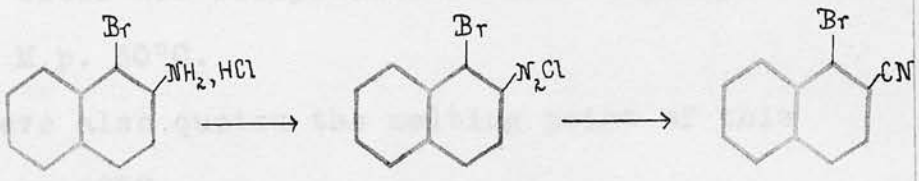


The hydrolysis to the free base is described by Franzen and Eidis (loc. cit.). The hydrochloride of the base, however, was prepared in this case, following the method of J. L. Grieve (loc. cit.) using concentrated hydrochloric acid as the hydrolysing agent.

Yield: 95 - 100% (from 20 gm. naphthalide)

M.p. 219° - 220°C (decomp.)

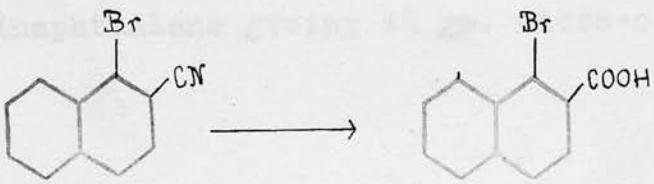
d) 1-Bromo-2-naphthonitrile.



Bromonaphthylamine hydrochloride (50 gm.) was diazotised in the usual way and the diazo solution treated with cuprous cyanide in the manner described by J. L. Grieve (loc. cit.). The nitrile was hydrolysed to the acid without preliminary purification.

Yields are not quoted by Grieve at this stage in the preparation.

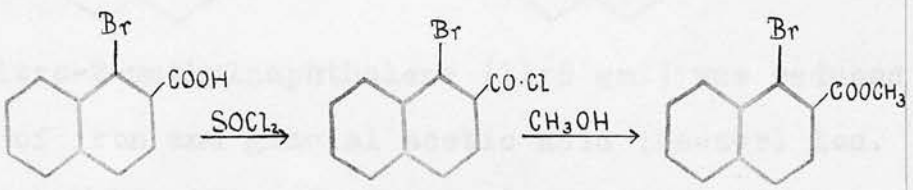
e) 1-Bromo-2-naphthoic acid.



The nitrile, on hydrolysis (J. L. Grieve, loc, cit.), gave 21 gm. acid (43%). M.p. 187 - 189°C.

It was found unnecessary to purify it for conversion to the ester.

Methyl 1-bromo-2-naphthoate.



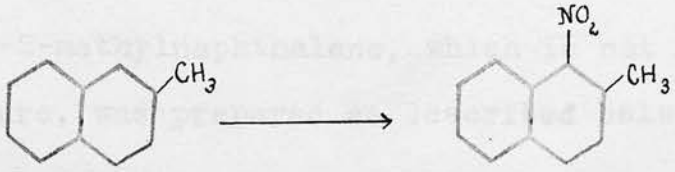
The esterification was carried out according to the method of J. L. Grieve (loc. cit.), 14 gm. ester being obtained from 15 gm. acid (90%).

The ester was recrystallised from light petroleum ether. M.p. 60°C.

Grieve also quotes the melting point of this compound as 60°C.

1-IODO-2-METHYLNAPHTHALENE.

a) 1-Nitro-2-methylnaphthalene.

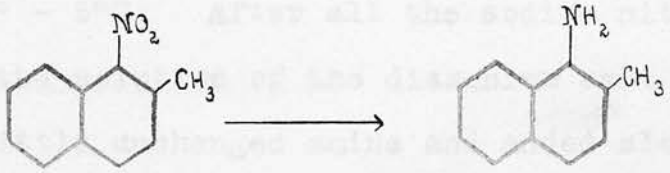


The nitration of β-methylnaphthalene was carried out as described by Lesser (Ann., 1913, 402, 31), 42·6 gm. β-methylnaphthalene giving 42 gm. nitro-compound.

Yield: 75%. M.p. 80°C.

Lesser quotes the yield as 40-50 gm.

b) 1-Amino-2-methylnaphthalene.



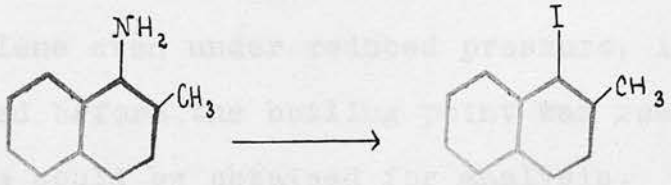
1-Nitro-2-methylnaphthalene (11·5 gm.) was reduced by means of iron and glacial acetic acid (Lesser, loc. cit.) and 6·0 gm. amine obtained.

Yield: 62%. M.p. 29° - 30°C.

Pure 1-amino-2-methylnaphthalene (m.p. 32°C) was deposited from light petroleum ether in long colourless needles.

Lesser quotes the yield as 60-70%, and the melting point as 32°C.

c) 1-Iodo-2-methylnaphthalene.



1-Iodo-2-methylnaphthalene, which is not listed in the literature, was prepared as described below.

7·2 gm. 1-amino-2-methylnaphthalene

16·5 cc. concentrated hydrochloric acid

3·0 gm. sodium nitrite (in 10 cc. water)

10·0 gm. potassium iodide (in 50 cc. water).

The amine was suspended in the hydrochloric acid, and the suspension cooled to 5°C. The solution of sodium nitrite was now run in drop by drop, the mixture being vigorously stirred and the temperature being maintained at 0° - 5°C. After all the sodium nitrite had been added the solution of the diazonium salt was filtered from a little unchanged amine and added slowly to the potassium iodide solution. The latter, during the addition, was cooled in ice. The dark-coloured solution which was formed, and from which nitrogen was evolved, was allowed to stand overnight, and the reaction completed by warming for a short time at 50°C. The dark oil which separated was extracted with ether and the ethereal solution well washed with dilute alkali, followed by water. The ether was boiled off and 1-iodo-2-methylnaphthalene obtained as a heavy dark oil.

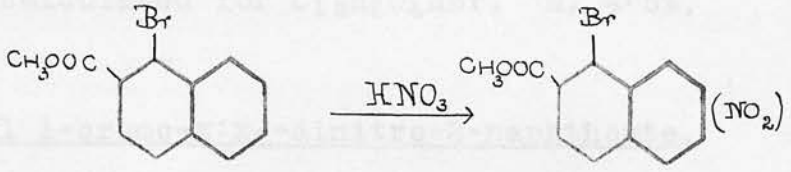
Yield: 5·1 gm. (42%).

It was found impossible to distil the crude iodomethylnaphthalene even under reduced pressure, iodine being liberated before the boiling point was reached. Thus no sample could be obtained for analysis. There was no doubt, however, as to its constitution. The method of synthesis, the presence of iodine, and the absence of nitrogen in the molecule, indicate its precise structure.

In these couplings where 1-iodo-2-methyl-naphthalene was used the compound was employed in the crude state.

It was anticipated, in the event of a successful coupling, that purification of the product would not be difficult.

Methyl 1-bromo-x-nitro-2-naphthoate.



6·4 gm. methyl -bromo-2-naphthoate.

15·0 cc. concentrated nitric acid.

The ester and nitric acid were placed in a small round-bottomed flask and the mixture stirred while the temperature was gradually raised to 60°C. This temperature was then maintained until all the solid had gone into solution. The latter was then poured onto ice and the semi-solid nitro-compound which separated taken up in ether. The ethereal solution, after washing with alkali and water, was dried over calcium chloride and the ether evaporated off. The yellow residual oil which remained was dissolved in boiling petroleum ether - benzene mixture (containing 80% petroleum ether, b.p. 60-80°C). On allowing this solution to stand overnight pale yellow crystals of the nitro-compound separated out and were filtered off and dried.

Yield: 3·4 gm. (45%). M.p. 108-115°C.

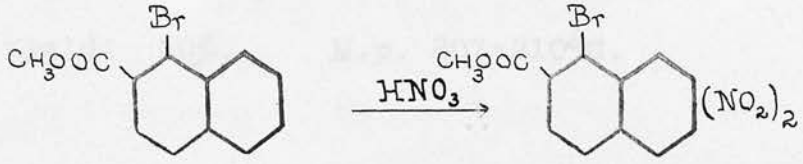
Pure methyl 1-bromo-x-nitro-2-naphthoate was obtained in pale yellow needles on two further recrystallisations from the petroleum ether - benzene mixture.

M.p. 120-121°C.

Analysis: found, N,4·6%:

calculated for $C_{12}H_8O_4NBr$, N, 4·5%.

Methyl 1-bromo-x:x_1-dinitro-2-naphthoate.



6·0 gm. methyl 1-bromo-2-naphthoate.

20 cc. fuming nitric acid (S.G. 1·5).

The nitric acid was cooled to 5°C and stirred while the ester was introduced in small portions over a period of five minutes. The dark solution which was produced was allowed to stand for ten minutes at room temperature and then poured into water. The yellow compound which separated was filtered off, washed with cold water, and dried.

Yield: 6·0 gm. (86%). M.p. 140-150°C.

The pure nitro-ester was obtained in pale yellow needles after two recrystallisations from ethyl acetate.

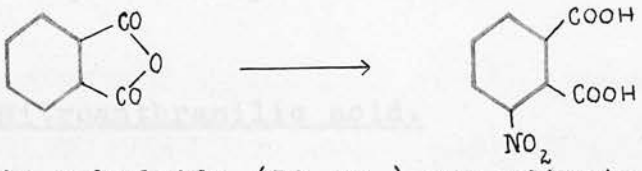
M.p. 168°-169°C.

Analysis: found, N, 7·9%;

calculated for $C_{12}H_7O_6N_2Br$, N, 7·9%.

2-IODO-3-NITROBENZOIC ACID.

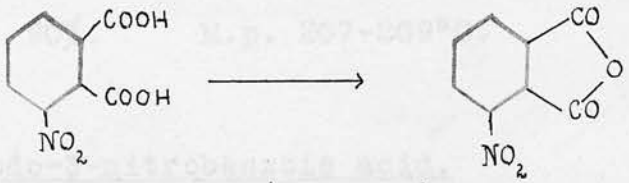
a) 3-Nitrophthalic acid.



Phthalic anhydride (50 gm.) was nitrated according to the method of Lawrence (J.A.C.S., 1920, 42, 1872) and 20 gm. 3-nitrophthalic acid obtained.

Yield: 30%. M.p. 207-210°C.

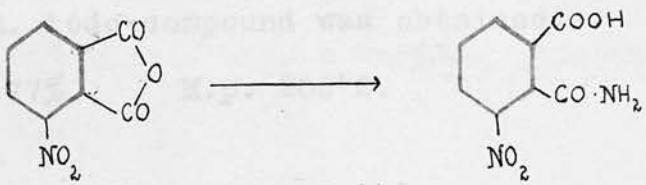
b) 3-Nitrophthalic anhydride.



3-Nitrophthalic acid (100 gm.) gave, on treatment with acetic anhydride (Clark, Organic Syntheses, Vol. 7, Page 74), 75 gm. anhydride.

Yield: 85%. M.p. 163-164°C.

c) 3-Nitrophthalamic acid.

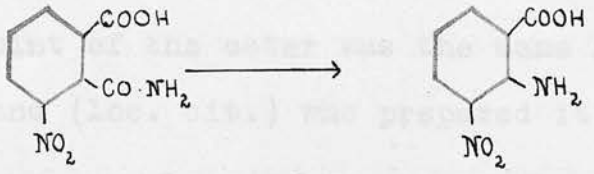


3-Nitrophthalic anhydride (70 gm.), on treatment

with ammonia and hydrochloric acid in the manner described by W. S. Haldane (Thesis, Edinburgh, 1934) gave rise to 52 gm. 3-nitrophthalamic acid.

Yield: 69%. M.p. 169-174°C.

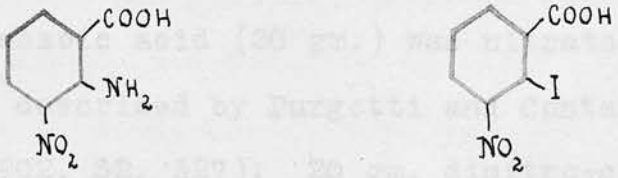
d) 3-Nitroanthranilic acid.



The treatment of 50 gm. 3-nitrophthalamic acid with sodium hypochlorite solution (W. S. Haldane, loc. cit.) produced 40 gm. 3-nitroanthranilic acid.

Yield: 90%. M.p. 207-209°C.

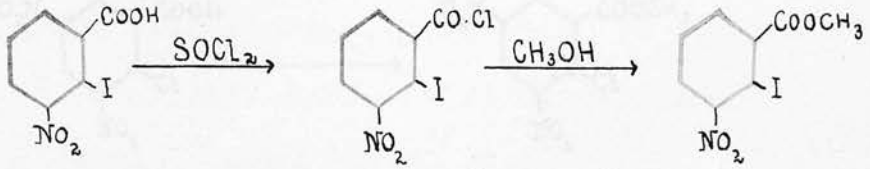
e) 2-Iodo-3-nitrobenzoic acid.



3-Nitroanthranilic acid (20 gm.) was diazotised according to the method of James, Kenner and Stubbing (J,C.S., 1920, 773) and a solution of potassium iodide added; 25 gm. iodo-compound was obtained.

Yield: 77%. M.p. 206°C.

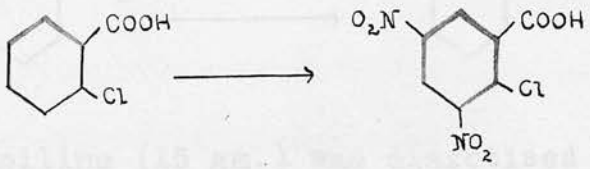
Methyl 2-iodo-3-nitrobenzoate.



2-Iodo-3-nitrobenzoic acid (20 gm.) was treated with thionyl chloride and methyl alcohol and 18·5 gm. ester obtained (after recrystallisation from alcohol). The melting point of the ester was the same as that quoted by W. S. Haldane (loc. cit.) who prepared it by the same method.

Yield: 88%.

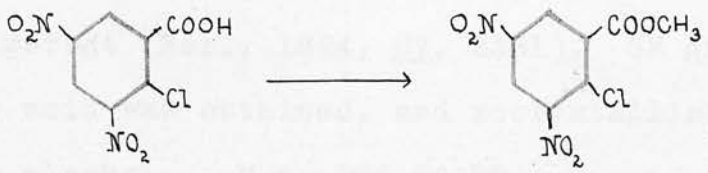
2-Chloro-3:5-dinitrobenzoic acid.



O-Chlorobenzoic acid (20 gm.) was nitrated under the conditions described by Purgotti and Contardi (Gaz. Ital. Chim., 1902, 32, 527); 20 gm. dinitro-compound was obtained. M.p. 194-196°C.

Purgotti and Contardi quote a melting point of 198·5°C. After three recrystallisations of the above product from 50% acetic acid a melting point of 199° - 200°C was obtained.

Methyl 2-chloro-3:5-dinitrobenzoate.

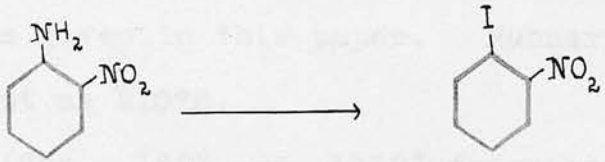


On esterification of the acid (20 gm.) in the usual manner with thionyl chloride and methyl alcohol (W. S. Haldane, loc. cit.) 16 gm. ester was produced.

Yield: 76%. M.p. (after recrystallisation from petroleum ether, b.p. 80°-100°C) 90°C.

W. S. Haldane quotes 90·5°C as the melting point of the ester.

o-Iodonitrobenzene.



o-Nitroaniline (15 gm.) was diazotised and the diazo solution added to a solution of potassium iodide as described by Ullmann (Ber., 1896, 29, 1880); 22 gm. o-iodonitrobenzene was obtained.

Yield: 85%. M.p. 49·5-50°C.

4-IODO-3-NITROBENZOIC ACID.

a) p-Iodobenzoic acid.



p-Aminobenzoic acid (36 gm.) was diazotised and potassium iodide solution added in the manner described by Willgerodt (Ber., 1894, 27, 2331); 52 gm. p-iodobenzoic acid was obtained, and recrystallised from aqueous alcohol. M.p. 265-266°C.

The melting point is quoted in Heilbron's "Dictionary of Organic Compounds" as 270°C.

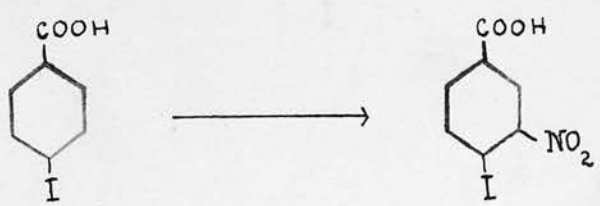
Yield: 79%.

b) 4-Iodo-3-nitrobenzoic acid.

4-Iodo-3-nitrobenzoic acid was first obtained by Hubner (Ber., 1875, 8, 562) by heating p-iodobenzoic acid with fuming nitric acid. No experimental details, however, are given in this paper. Hubner quotes the melting point as 210°C.

Allen (Ber., 1893, 26, 1739) describes the preparation of 4-iodoso-3-nitrobenzoic acid by the prolonged action of fuming nitric acid on p-iodobenzoic acid. Allen quotes the melting point of the iodoso-compound as 190°-205°C.

During the present work it was found that 4-iodo-3-nitrobenzoic acid could be prepared in excellent yield by the action of fuming nitric acid on p-iodobenzoic acid under carefully controlled conditions. The preparation is described below.



14 gm. p-iodobenzoic acid

100 cc. fuming nitric acid.

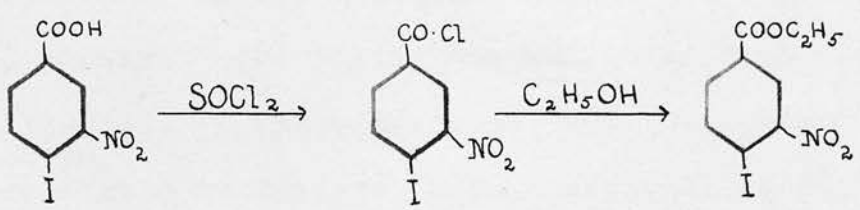
The iodobenzoic acid and the nitric acid were placed in a small flask and the mixture vigorously stirred while the temperature was slowly raised to 50°C. The iodobenzoic acid went into solution, and the latter was maintained at 50°C for three minutes. It was then poured into water and the pale yellow nitro-compound filtered off, well washed with water, and dried.

Yield: 15·6 gm. (94%). M.p. 209-211°C.

On crystallisation from a mixture of glacial acetic acid and water (1:1) the nitro-iodobenzoic acid was obtained in the form of slender yellow needles of melting point 212-213°C.

Ethyl 4-iodo-3-nitrobenzoate.

The ethyl ester of 4-iodo-3-nitrobenzoic acid was prepared by Allen (loc. cit.) by treatment of the acid with ethyl alcohol and hydrochloric acid gas. A more satisfactory method was found in the employment of thionyl chloride and ethyl alcohol.



10 gm. 4-iodo-3-nitrobenzoic acid

60 cc. purified thionyl chloride

60 cc. absolute alcohol.

The acid and thionyl chloride were boiled under reflux on the water bath for thirty minutes, by which time a clear yellow solution had been formed. The excess thionyl chloride was then distilled off under diminished pressure, the alcohol added to the cool residue, and the solution boiled for a further thirty minutes. The bulk of the alcohol was distilled off on the water bath, the ester taken up in ether, and the ethereal extract washed with dilute alkali followed by water. After drying over calcium chloride, the ethereal extract was evaporated to dryness and the ester obtained as a solid yellow residue.

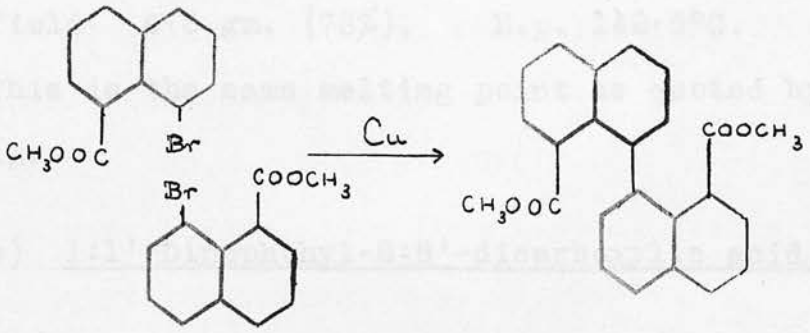
Yield: 9·0 gm. (85%). M.p. 84-88°C.

The ester crystallises in gleaming yellow needles from petroleum ether (b.p. 60-80°C). M.p. 90-91°C.

Allen (loc. cit.) quotes the melting point of the ester as 88°-89·5°C.

10:11-BENZOBENZANTHRONE-1'-CARBOXYLIC ACID.

a) Dimethyl 1:1'-dinaphthyl-8:8'-dicarboxylate.



In preparing this compound the method of Pursell (Thesis, Edinburgh, 1933) was somewhat modified and an increase in yield obtained.

13 gm. methyl 8-bromo-1-naphthoate

10 gm. copper bronze.

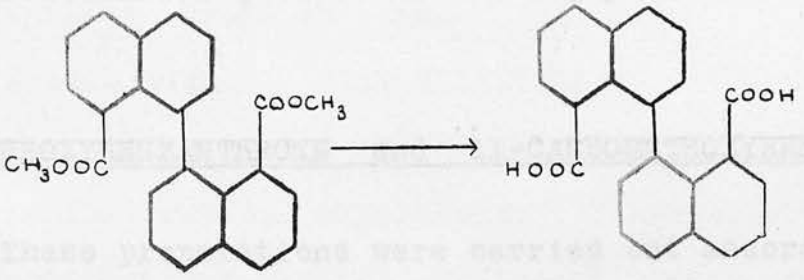
The ester was placed in a wide-necked flask of 150 cc. capacity which was equipped with a mechanical stirrer and heated on an oil-bath at 220°C, outside temperature. The stirrer was set in motion and the copper bronze slowly added over a period of thirty minutes. The stirring was continued for a further three hours at a temperature of 225-230°C. The flask was then cooled and the solid product ground to a fine powder in a mortar. The powder was extracted with boiling acetone (250 cc. in three portions) and the acetone extract evaporated to dryness, when a crystalline deposit

of the dinaphthyl dicarboxylate was obtained. This was recrystallised from petroleum ether (b.p. 100-120°C) and the pure crystalline product isolated.

Yield: 6·8 gm. (75%). M.p. 142·5°C.

This is the same melting point as quoted by Pursell.

b) 1:1'-Dinaphthyl-8:8'-dicarboxylic acid.

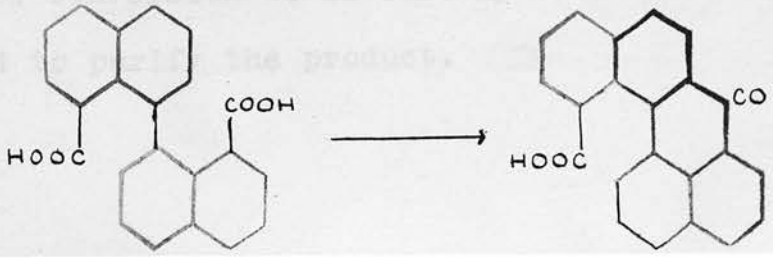


1:1'-Dinaphthyl-8:8'-dicarboxylic acid was obtained by Pursell (loc. cit.) by hydrolysis of the diester with alcoholic caustic potash. It was found, however, that a purer product, and a greater yield, was given by hydrolysis with amyl alcohol and potassium hydroxide (Stanley, J.A.C.S., 1931, 53, 3106).

Yield: 91%. M.p. 298-300°C.

The compound crystallises from alcohol as a buff-white powder of melting point 306-307°C.

c) 10:11-Benzobenzanthrone-1'-carboxylic acid.



The dinaphthyl dicarboxylic acid was cyclised to the benzobenzanthrone carboxylic acid by means of zinc chloride in glacial acetic acid solution (Friedlander, Ber., 1882, 15, 713) 8·5 gm. being obtained from 10 gm. dinaphthyl dicarboxylic acid.

Yield: 90%. M.p. 274-276°C.

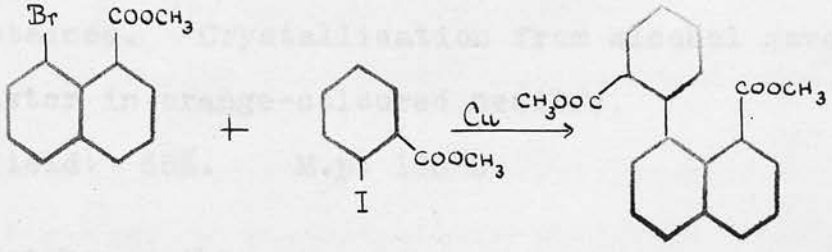
The acid crystallises from glacial acetic acid and alcohol in yellow prisms, m.p. 277-278°C.

Friedlander quotes the melting point as 278°C.

11-CARBOXYBENZANTHRONE and 11-CARBOMETHOXYBENZANTHRONE.

These preparations were carried out according to the method of Rule and co-workers (J., 1935, 573).

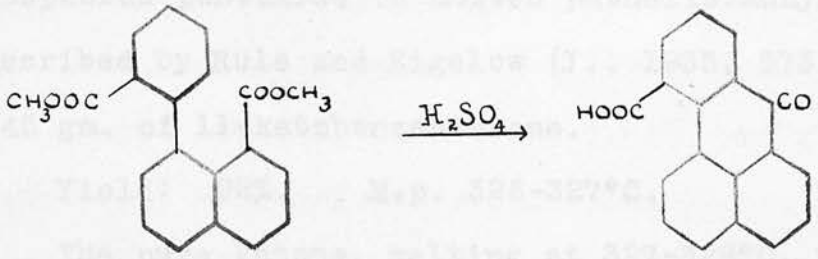
a) Methyl 8-(o-carbomethoxyphenyl)-1-naphthoate.



Methyl o-iodobenzoate (50 gm.) and methyl 8-bromo-1-naphthoate (25 gm.) were treated with copper powder at 175-180°C and 22·5 gm. of the phenylnaphthyl derivative obtained. M.p. 131-132°C.

For conversion to 11-carboxybenzanthrone there is no need to purify the product.

b) 11-Carboxybenzanthrone.



The mixed esters from a) (10 gm.) were treated with concentrated sulphuric acid at 100°C and 8·2 gm. 11-carboxybenzanthrone obtained.

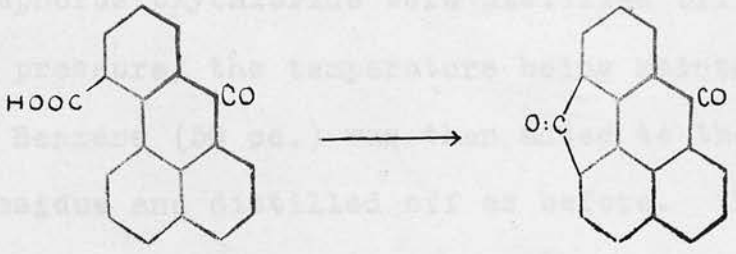
Yield: 71%. M.p. 271-272°C.

The yields quoted are based on the bromonaphthoate used in the previous experiment. 11-Carboxybenzanthrone crystallises from alcohol or glacial acetic acid in orange-yellow needles, melting at 273°C.

By carrying out the cyclisation of the mixed esters at 50°C instead of 100°C, 11-carbomethoxybenzanthrone was obtained. Crystallisation from alcohol gave the pure ester in orange-coloured needles.

Yield: 65%. M.p. 160°C.

1:11-Ketobenzanthrone.

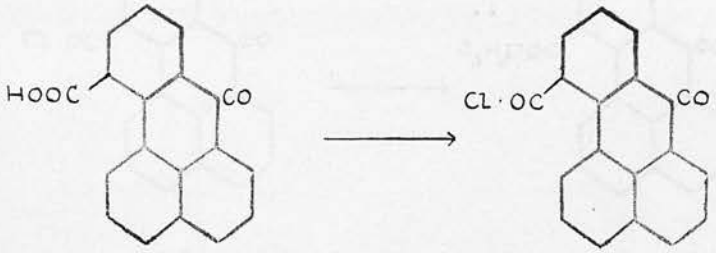


11-Carboxybenzanthrone (4 gm.) on treatment with phosphorus pentoxide in molten phthalic anhydride, as described by Rule and Bigelow (J., 1935, 573), gave 3·45 gm. of 11-ketobenzanthrone.

Yield: 92%. M.p. 325-327°C.

The pure ketone, melting at 327-328°C, was obtained in stout orange needles on crystallisation from glacial acetic acid.

Acid chloride of 11-carboxybenzanthrone.



2·5 gm. 11-carboxybenzanthrone

75 cc. dry benzene

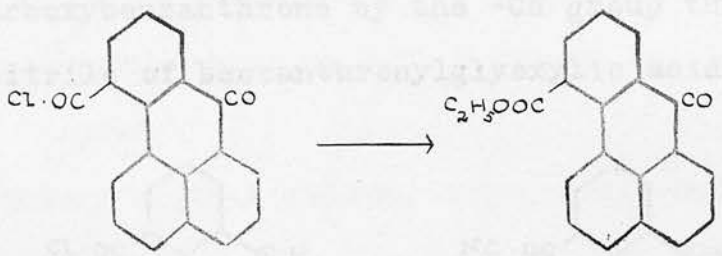
3·25 gm. purified phosphorus pentachloride.

The acid, benzene and phosphorus pentachloride were heated together on the water-bath at 40°C. The acid gradually dissolved and after thirty minutes the benzene and phosphorus oxychloride were distilled off under diminished pressure, the temperature being maintained below 45°C. Benzene (50 cc.) was then added to the greenish-brown residue and distilled off as before. The pale green solid which remained was not further purified for

use in any of the following reactions. The yield, as indicated by the figures given in the preparations below, was practically quantitative. M.p. 145-150°C.

Boyes (Thesis, Edinburgh, 1936), who first prepared this acid chloride, and whose method has been slightly modified here, quotes the melting point as 154-156°C.

Ethyl benzanthrone-11-carboxylate.



2·5 gm. 11-carboxybenzanthrone
25 cc. absolute alcohol.

The 11-carboxybenzanthrone was converted to acid chloride as outlined above, and the alcohol added to the solid residue. The solution was then heated under reflux for two hours. By allowing it to cool a mass of fine yellow hair-like needles separated and were filtered off and dried.

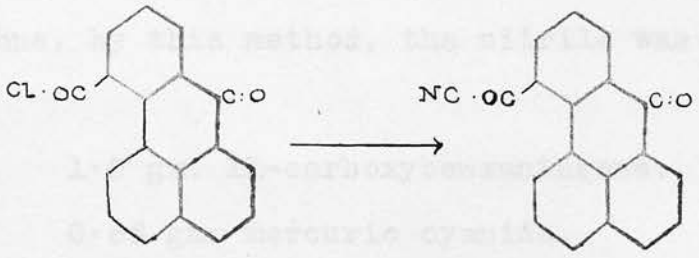
Yield: 2·25 gm. (82%). M.p. 154-156°C.

The pure ethyl ester crystallises from alcohol in gleaming yellow needles. M.p. 159°C.

Analysis: found, C, 79·1%, H, 5·0%:
calculated for $C_{20}H_{14}O_3$, C, 79·5%, H, 4·6%.

ATTEMPTS TO PREPARE THE NITRILE OF BENZANTHRONYLGLYOXYLIC ACID: THE ANHYDRIDE OF 11-CARBOXYBENZANTHRONE.

In the experiments described below attempts were made to replace the chlorine in the acid chloride of 11-carboxybenzanthrone by the -CN group thus forming the nitrile of benzanthronylglyoxylic acid.



I) 1·0 gm. 11-carboxybenzanthrone.
0·5 gm. cuprous cyanide.
50 cc. benzonitrile.

The 11-carboxybenzanthrone was converted to the acid chloride in the manner described on page 95 and the latter dissolved in the benzonitrile. Cuprous cyanide was added to the green solution and the mixture heated under reflux on an oil-bath for three hours. The benzonitrile was distilled off in steam and the brownish-

yellow residue filtered off, washed well with water and dried.

Yield: 0·92 gm. M.p. 255°-265°C.

This substance was almost completely soluble in alkali, and, by this means, was separated into two fractions a) and b);

a) 0·80. alkali-soluble compound which proved, on examination, to be 11-carboxybenzanthrone.

b) 0·06 gm. alkali-insoluble compound which had no melting point below 360°C. This substance, probably a condensation product of some type, was not investigated further.

Thus, by this method, the nitrile was not obtained.

II) 1·0 gm. 11-carboxybenzanthrone.
0·65 gm. mercuric cyanide.
37 cc. dry benzene (A.R.).

The 11-carboxybenzanthrone was converted to acid chloride as in the previous experiment, and the acid chloride taken up in the benzene. The acid chloride, mercuric cyanide, and benzene were then boiled under reflux for fourteen hours and the benzene distilled off under diminished pressure. The residue was digested with alkali for a few minutes at 60°C and the alkaline solution filtered. On acidification of the solution 0·15 gm. 11-carboxybenzanthrone was recovered.

The alkali-insoluble product of the reaction weighed 0·80 gm. and melted at 245°-255°C with some preliminary sintering. On recrystallisation from anisole several times the melting point ultimately became sharp at 276°-277°C. This substance, however, was found to be devoid of nitrogen and thus could not be the nitrile of benzanthronylglyoxylic acid. It was proved, as is shown below, to be the anhydride of 11-carboxybenzanthrone.

III) A method employed by Claisen (Ber., 1898, 31, 1024) to prepare ketonitriles was next attempted in this special case. The method consists in treating an acid chloride with anhydrous hydrogen cyanide in dry ether at room temperature. Dry pyridine is introduced into this mixture to remove the hydrochloric acid formed in the reaction

$$R\cdot COCl + H\cdot CN \longrightarrow R\cdot COCN + HCl$$

4 gm. 11-carboxybenzanthrone
250 cc. dry ether
2 gm. anhydrous hydrogen cyanide
3 gm. anhydrous pyridine.

The acid chloride of 11-carboxybenzanthrone was prepared in the usual way and suspended in the dry ether. The hydrogen cyanide was added and the pyridine (dissolved in 20 cc. dry ether) slowly introduced from

a dropping funnel. The mixture was shaken continuously during the addition and then allowed to stand for twenty-four hours at room temperature. During this period the mixture was shaken vigorously at intervals. The acid chloride went slowly into solution and a yellow substance was deposited on the walls of the flask. The bulk of the ether was now evaporated off and the yellow residue heated for a few minutes with dilute caustic soda solution at 60°C. The solution was filtered, the filtrate acidified with dilute sulphuric acid, and the yellow solid filtered off. This weighed 0·5 gm. and was found to be 11-carboxybenzanthrone.

The alkali-insoluble reaction product weighed 3·2 gm. and melted at 260° - 265°C. On recrystallisation from anisole the melting point was raised to 277°C. A mixed melting point with the product obtained from the previous reaction (acid chloride and mercuric cyanide) showed no depression and thus indicated the identity of the two products.

An analysis was carried out and the following figures obtained

C, 81·1%, H, 3·75%.

The absence of nitrogen in the compound obtained as above ruled out the possibility of its being the nitrile of benzanthronylglyoxylic acid. Its insolubility in alkali, and the analysis figures suggested that, in the

above reactions, the hitherto unknown anhydride of 11-carboxybenzanthrone had been prepared. The calculated percentages of carbon and hydrogen in this substance are:

C, 81·5%, H, 3·4%.

In an endeavour to confirm this view resort was made to the following considerations.

On treatment of an acid anhydride with sodium ethoxide solution under suitable conditions, equivalent amounts of the sodium salt of the parent acid and the ethyl ester of the acid are produced. An attempt was made to see whether the compound in question would behave in this manner.

Treatment of the alkali-insoluble compound with alcoholic sodium ethoxide.

0·20 gm. alkali-insoluble compound.
250 cc. ethyl alcohol.
20 cc. alcoholic sodium ethoxide solution (0·01792 N)

The above were heated under reflux for four hours by which time the alkali-insoluble compound had gone completely into solution. The alcohol was then distilled off until the volume of the solution had diminished to about 30 cc. An excess of water was now added and a yellow

solid precipitated. This was filtered off, washed with water, and dried.

Weight: 0·10 gm. M.p. 154°-156°C.

This substance crystallised from ethyl alcohol in fine yellow hair-like crystals of melting point 159°C. It showed no depression in melting point when mixed with ethyl benzanthrone 11-carboxylate.

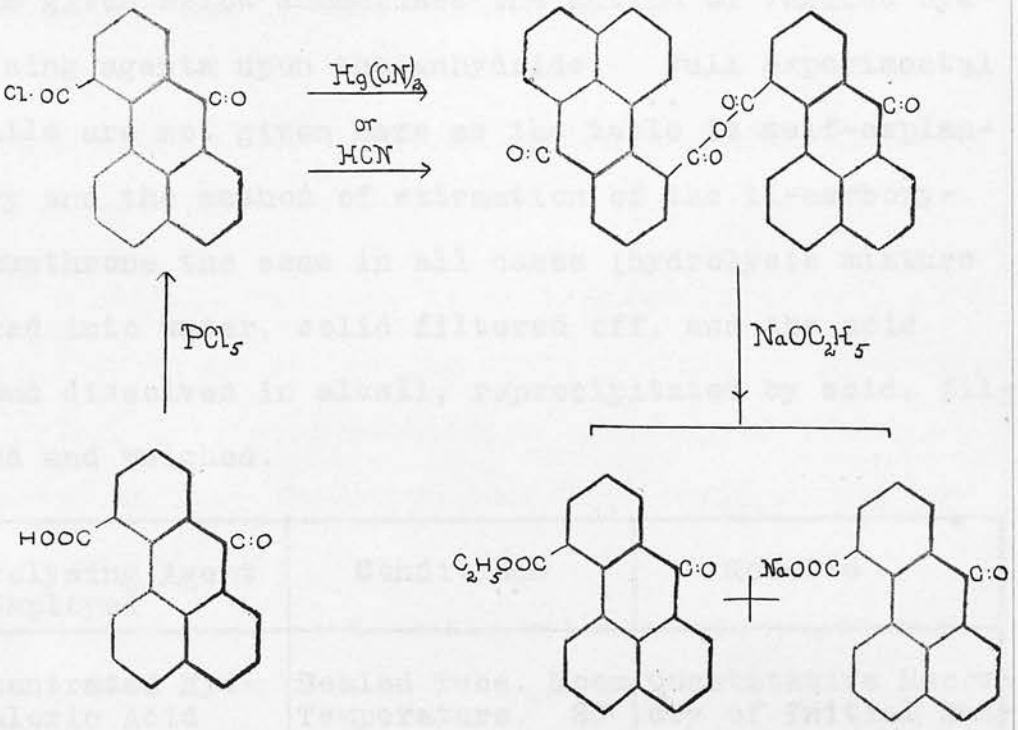
The filtrate from the above was acidified with dilute sulphuric acid, the yellow precipitate filtered off, washed with water and dried.

Weight: 0·09 gm. M.p. 269°-272°C.

On examination this compound was found to be 11-carboxybenzanthrone (melting point and mixed melting point).

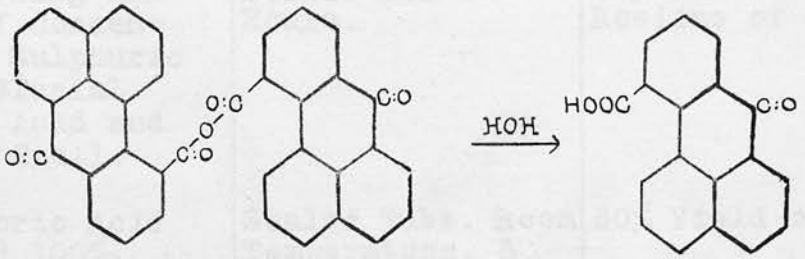
Thus, as had been expected, the alkali-insoluble compound prepared by the action of mercuric cyanide or of hydrogen cyanide on the acid chloride of 11-carboxybenzanthrone, on treatment with sodium ethoxide solution, yielded equivalent amounts of the sodium salt of 11-carboxybenzanthrone and ethyl benzanthrone-11-carboxylate. And so it was proved to be the hitherto unknown anhydride of 11-carboxybenzanthrone.

The scheme below illustrates the course of these reactions.



Hydrolysis of the Anhydride of 11-Carboxybenzanthrone.

On hydrolysis the anhydride of 11-carboxybenzanthrone is converted to the parent acid.



The rate and the extent of the hydrolysis is, of

course, dependent upon the hydrolysing agent used. The table given below summarises the action of various hydrolysing agents upon the anhydride. Full experimental details are not given here as the table is self-explanatory and the method of extraction of the 11-carboxybenzanthrone the same in all cases (hydrolysis mixture poured into water, solid filtered off, and the acid formed dissolved in alkali, reprecipitated by acid, filtered and weighed.

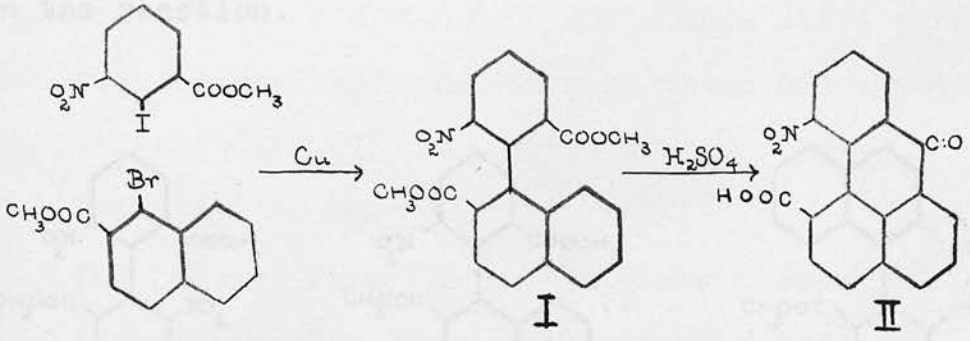
Hydrolysing Agent Employed	Conditions	Results
Concentrated Hydrochloric Acid	Sealed Tube. Room Temperature. 20 Days.	Quantitative Recovery of Initial Material.
do.	Sealed Tube. Room Temperature. 200°C. 24 hours.	80% Yield of Acid.
Concentrated Sulphuric Acid	Room Temperature. 6 Hours.	90% Yield of Acid.
do.	Heated on Water-bath. 90 Minutes.	Almost Quantitative Yield of the Acid.
Hydrolysing Mixture of Concentrated Sulphuric Acid, Glacial Acetic Acid and Water; 2:4:1.	Boiled for 6 Hours.	70% Yield of Acid. Residue of Carbon.
Phosphoric Acid (H_3PO_4) 100%.	Sealed Tube. Room Temperature. 8 Days.	60% Yield of Acid.
do.	Sealed Tube. 80°-90°C. 3 Hours.	70% Yield of Acid.

Unless otherwise stated, the product of these reactions, other than 11-carboxybenzanthrone, is the original anhydride.

THE ATTEMPTED PREPARATION OF VARIOUS 1:11-DISUBSTITUTED BENZANTHRONES BY THE ULLMANN SYNTHESIS.

I) Attempted Preparation of 11-Nitro-1-carboxybenzanthrone.

An attempt was made to synthesise 11-nitro-1-carboxybenzanthrone by heating methyl 2-iodo-3-nitrobenzoate and methyl 1-bromo-2-naphthoate with copper bronze in the expectation that these two compounds would couple together to form the phenylnaphthyl derivative (I). The latter would then be cyclised with concentrated sulphuric acid to give the benzanthrone (II).



2·0 gm. methyl 1-bromo-2-naphthoate (1 mol.).

4·8 gm. methyl 2-iodo-3-nitrobenzoate (2 mol.).

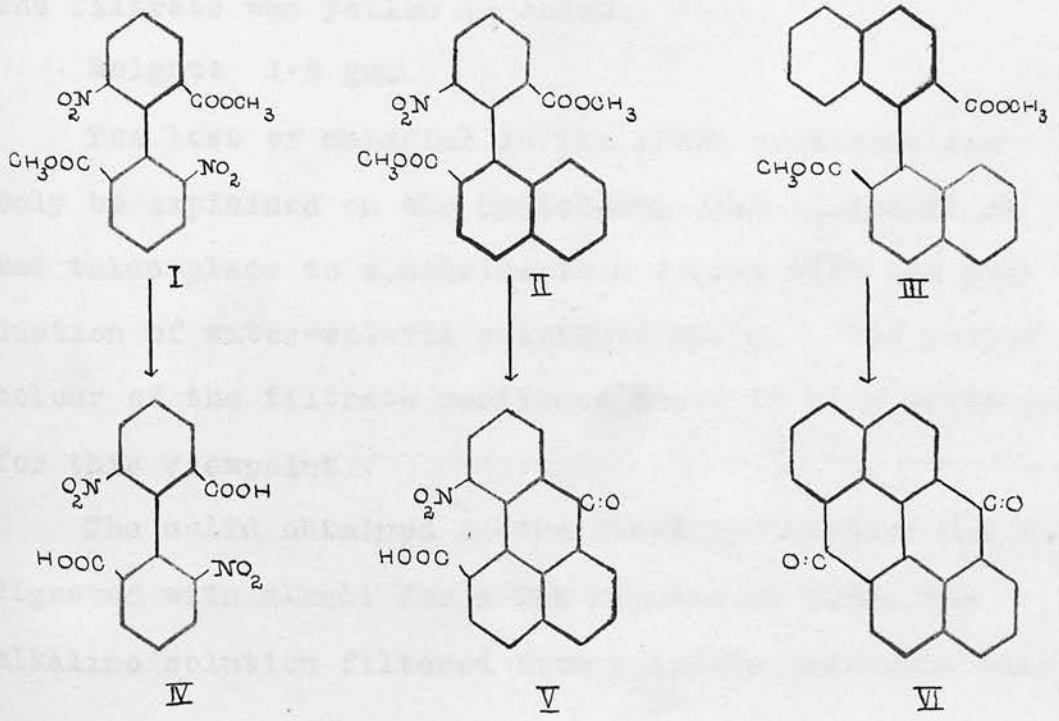
2·4 gm. copper bronze.

The mixed esters were heated with stirring to 185°-190°C and the copper added in portions over a period of forty-five minutes. The temperature was then allowed to rise to 200°C and maintained at this figure for a

further four hours. The reaction product was extracted with 25 cc. acetone (in three portions) and the inorganic matter filtered off. The acetone was then distilled off on the water-bath and the last traces removed by distillation in vacuo. Ether (3 cc.) was added to the warm oily residue and the brownish crystals which deposited were filtered off, washed with a little ether, and dried.

Weight: 4·0 gm. M.p. 112-122°C.

This product could not be crystallised from petroleum ether and presumably consisted of a mixture of the diphenyl (I), phenylnaphthyl (II), and dinaphthyl derivatives (III) which theoretically may all be formed in the reaction.



It was decided to treat the crude ester mixture with concentrated sulphuric acid in the hope that the cyclisation would yield a mixture of IV,V, and VI, the diphenic acid, the benzanthrone carboxylic acid, and anthanthrone. Alkaline extraction would then allow the anthanthrone to be filtered off, and an acid mixture obtained. Fractional crystallisation of the latter might then give a separation.

4 gm. mixed esters.
40 cc. concentrated sulphuric acid.

The mixed esters were heated with the sulphuric acid for one hour at 100°C with stirring and the green solution poured into water. The orange solid thrown down was filtered off, washed with water and dried. The filtrate was yellow in colour.

Weight: 1·5 gm.

The loss of material in the above treatment can only be explained on the hypothesis that sulphonation had taken place to a considerable extent with the production of water-soluble sulphonic acids. The yellow colour of the filtrate mentioned above is also evidence for this viewpoint.

The solid obtained in the above cyclisation was now digested with alkali for a few minutes at 60°C, the alkaline solution filtered from a little insoluble mat-

erial, and the filtrate acidified with dilute sulphuric acid. The brown solid precipitated was filtered off, washed with water and dried.

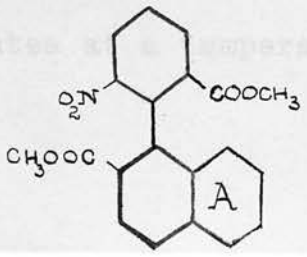
The alkali-insoluble fraction of the above digestion (0·1 gm.) proved to be anthanthrone; the alkali-soluble fraction (1·3 gm.) melted at 260°-265°C and gave no red benzanthrone colour in concentrated sulphuric acid. It was recrystallised from dilute acetic acid. The gleaming light brown plates melted at 269°-271°C. It was presumed to be 6:6'-dinitrodiphenyl-2:2'-dicarboxylic acid (melting point quoted in Heilbron's "Dictionary of Organic Compounds" as 263°C.). This was confirmed by analysis.

Analysis: found, C, 50·3%, H, 2·2%, N,8·5%:

calculated for $C_{14}H_8O_8N_2$, C, 50·6%, H, 2·4%, N, 8·4%.

The yield of this acid, calculated on the initial iodobenzoate used, was 52%.

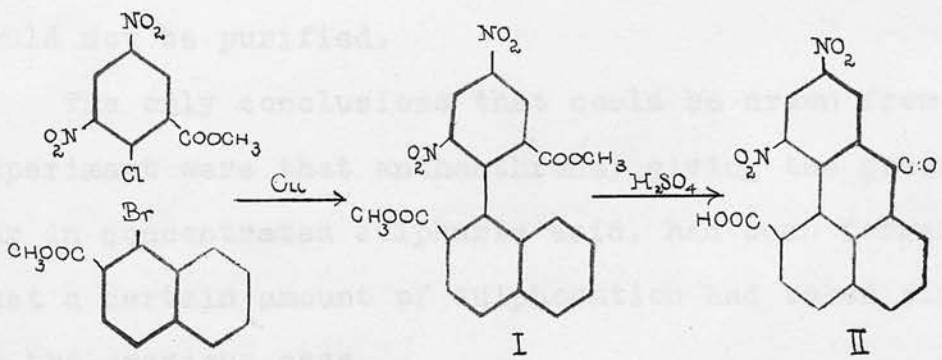
From the results of this experiment it was concluded that, in addition to the formation of the diphenyl derivative, and the dinaphthyl derivative, coupling also took place in the Ullmann reaction to produce the phenylnaphthyl derivative. The latter, however, on treatment with concentrated sulphuric acid, was sulphonated, presumably in the unprotected naphthalene ring A, and converted to a water-soluble benzanthrone sulphonic acid.



Another experiment was carried out similar to the last, the temperature at which the copper was introduced, however, being 200°C. A precisely similar result was obtained.

II) Attempted Preparation of 9:11-Dinitro-1-carboxybenzanthrone.

In this experiment an attempt was made to couple methyl 2-chloro-3:5-dinitrobenzoate and methyl 1-bromo-2-naphthoate in the presence of copper bronze, and to cyclise the product obtained (I) with concentrated sulphuric acid to yield 9:11-dinitro-1-carboxybenzanthrone (II).



2·0 gm. methyl 2-chloro-3:5-dinitrobenzoate (1 mol.).

2·0 gm. methyl 1-bromo-2-naphthoate (1 mol.).

2·4 gm. copper bronze.

This Ullmann reaction was carried out in the usual manner, the copper being introduced over a period of forty-five minutes at a temperature of 200°C. After a

further four hours at this temperature the organic matter was extracted with acetone, and the acetone then distilled off. Ether (3 cc.) was added to the dark oily residue but no crystallisation took place. Even on standing for several days at 0°C the oil failed to solidify or deposit crystals. It was decided to treat this oil with sulphuric acid and attempt to purify the products of this treatment. The oil was heated at 100°C with 25 cc. concentrated sulphuric acid for half-an-hour, stirring being maintained throughout. The brownish-green solution was then poured into water and the dark solid precipitated filtered off. The filtrate was dark brown in colour, indicating sulphonation. The solid formed a black slime on the filter paper which could not be purified.

The only conclusions that could be drawn from this experiment were that anthanthrone, giving the green colour in concentrated sulphuric acid, had been formed; and that a certain amount of sulphonation had taken place as in the previous case.

The next experiment details how an attempt was made to overcome the difficulties encountered in the two last Ullmann reactions.

III Attempted Preparation of 11:x-Dinitro-1-carboxybenzanthrone; Dimethyl x:x'-dinitro-1:1'-dinaphthyl-2:2'-dicarboxylate.

In the two previous reactions material was lost due to sulphonation of the reaction products. The sulphonation presumably took place in the unsubstituted part of the molecule.

To avoid this difficulty methyl 1-bromo-2-naphthoate was nitrated and a mono-nitro derivative obtained. It was presumed that the presence of the nitro-group would inhibit further substitution in the product of the coupling on treatment with sulphuric acid.

The preparation of the nitro-compound is described on page 82.

Experiment.

1·5 gm. methyl 1-bromo-x-nitro-2-naphthoate (1 mol.).

1·5 gm. methyl 2-iodo-3-nitrobenzoate (1 mol.).

1·6 gm. copper bronze.

The mixed esters were heated with stirring at 190°-195°C and the copper added in portions over a period of thirty minutes. The temperature was then raised to 200°-205°C and maintained there for three hours. The organic material was extracted with acetone as before, the acetone distilled off, and ether added to the oily residue. A

dark mass separated out and was filtered off and washed with a little ether.

Weight: 0·5 gm. M.p. 226-236°C.

This product was very dark in colour and could not at first be recrystallised satisfactorily. Initial treatment by the adsorption method, however, was efficacious in removing a dark-coloured impurity. This initial treatment is described on page 157.

The product of the adsorption, after two crystallisations from glacial acetic acid, melted sharply at 250°C. It gave a green colour on treatment with concentrated sulphuric acid at the boiling point. This colour, an indication of anthanthrone formation, gave rise to the view that the product of the above Ullmann reaction was a dinaphthyl derivative, being indeed the hitherto unknown but still incompletely oriented dimethyl x:x'-dinitro-1:1'-dinaphthyl-2:2'-dicarboxylate.

Confirmation was supplied by analysis.

Analysis: found, C, 62·0%, H, 3·85%:

calculated for $C_{24}H_{16}O_8N_2$, C, 62·6%, H, 3·5%.

The yield of dinaphthyl derivative, calculated on the basis of initial bromo-nitronaphthoate used, was 45%.

From the result of this experiment it would appear that the reactivity of the bromine in methyl 1-bromo-x-nitro-2-naphthoate is considerably greater than that of the bromine in methyl 1-bromo-2-naphthoate itself. This

increased reactivity has apparently caused methyl 1-bromo-x-nitro-2-naphthoate to couple, in presence of copper, almost exclusively with itself. No coupling of the naphthalene compound with the benzene derivative to produce a phenylnaphthyl dicarboxylate was detected, nor was any diphenyl dicarboxylate found.

On heating dimethyl x:x'-dinitro-1:1'-dinaphthyl-2:2'-dicarboxylate with sulphuric acid at the boiling point for a few minutes and pouring the green solution into water, a dark precipitate of x:x'-dinitroanthanthrone was obtained. This was filtered off. Although no attempt at purification was made it was identified as an anthanthrone, forming a red-violet vat with alkaline hydrosulphite, which dyed cotton in brown shades, fast towards alkali and acid. Evidently under the reducing conditions employed the nitro-groups had escaped attack.

Dimethyl x:x_1:x':x_1'-tetranitro-1:1'-dinaphthyl-2:2'-dicarboxylate.

During tentative experiments on the nitration of methyl 1-bromo-2-naphthoate a dinitro-compound was obtained. This dinitro-compound was heated with methyl 2-iodo-3-nitrobenzoate in presence of copper bronze in the hope that a phenylnaphthyl derivative would be obtained. The only compound isolated from the coupling

,however, was a dinaphthyl, methyl x:x_1:x':x_1'-tetranitro-1:1'-dinaphthyl-2:2'-dicarboxylate.

Experiment.

0·9 gm. methyl 1-bromo-x:x_1-dinitro-2-naphthoate (1 mol.).
0·9 gm. methyl 2-iodo-3-nitrobenzoate (1 mol.).
1·0 gm. copper bronze.

The esters were heated with stirring at 210°C and the copper added in portions (twenty minutes). The temperature was raised and maintained at 220°C for three hours. The organic matter was extracted with acetone, the acetone evaporated off, and ether added to the residue. The light brown solid which separated out on standing was filtered off and washed with a little ether.

Weight: 0·65 gm. M.p. 260°-270°C.

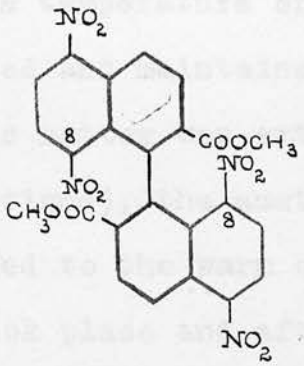
As in the case of dimethyl x:x'-dinitro-1:1'-dinaphthyl-2:2'-dicarboxylate, the product of this reaction was submitted to a preliminary purification by the adsorption method before recrystallisation from glacial acetic acid. The pure product crystallised in brownish-yellow micro-crystalline plates of melting-point 333°-334°C.

The compound gave no trace of green colour in boiling concentrated sulphuric acid but was proved to be a dinaphthyl derivative by the results of a nitrogen analysis.

Analysis: found, N, 9·9%;

calculated for $C_{24}H_{14}O_{12}N_4$, N, 10·2%.

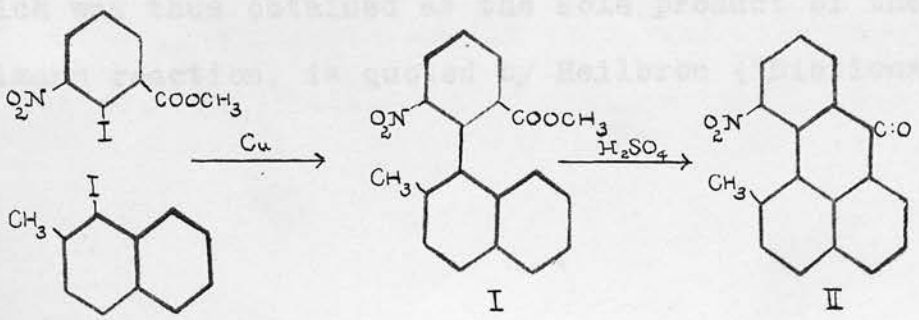
The failure to effect cyclisation in this case may be due to one of the substituting nitro-groups being in the position 8 (below) in the original naphthalene compound.



The yield of dinaphthyl derivative in this case is 93% calculated on the initial bromo-naphthoate used.

IV) Attempted Preparation of 11-Nitro-1-methylbenzanthrone.

In this experiment it was proposed to couple methyl 2-iodo-3-nitrobenzoate and 1-iodo-2-methylnaphthalene by means of the Ullmann reaction, and to cyclise the phenylnaphthyl derivative (I) formed to 11-nitro-1-methylbenzanthrone (II).



2·4 gm. 1-iodo-2-methylnaphthalene (1 mol.).

2·8 gm. methyl 2-iodo-3-nitrobenzoate (1 mol.).

3·0 gm. copper bronze.

This Ullmann reaction was carried out as in the previous cases. The copper was introduced over a period of one hour at a temperature of 160°C. The temperature was then raised and maintained at 180°C for four hours. The organic matter was extracted with acetone (30 cc. in four portions), the acetone taken off as before and 3 cc. ether added to the warm oily residue. Crystallisation soon took place and after standing for 48 hours at 0°C the light brown crystals were filtered off, washed with a little ether, and dried.

Yield: 1·4 gm. M.p. 127-128°C.

On two recrystallisations of this substance from ligroin light brown plates were obtained of melting point 130°C. The substance did not give any red colour in concentrated sulphuric acid but was hydrolysed to an acid of melting point 269°-271°C. This latter was shown to be 2:2'-dinitrodiphenyl-6:6'-dicarboxylic acid by a mixed melting point with an authentic specimen obtained in a previous experiment.

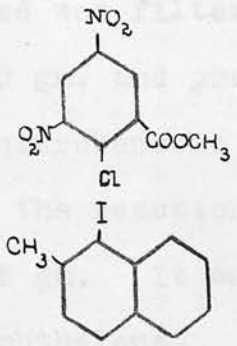
Dimethyl 2:2'-dinitrodiphenyl-6:6'-dicarboxylate, which was thus obtained as the sole product of the above Ullmann reaction, is quoted by Heilbron ("Dictionary of

Organic Compounds") as melting at 130°-131°C.

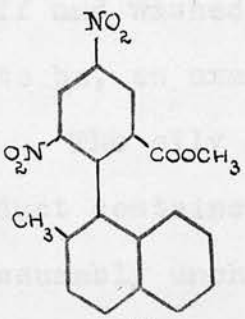
The yield obtained was 85% of the theoretical.

V) Attempted Preparation of 9:11-Dinitro-1-methylbenzanthrone.

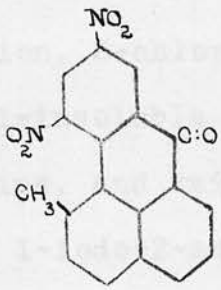
Here an attempt was made to couple methyl 2-chloro-3:5-dinitrobenzoate and 1-iodo-2-methylnaphthalene by the usual method. The phenylnaphthyl derivative (I) formed would then be cyclised to yield 9:11-dinitro-1-methylbenzanthrone (II).



I



I



II

3·4 gm. methyl 2-chloro-3:5-dinitrobenzoate (1 mol.).

3·4 gm. 1-iodo-2-methylnaphthalene (1 mol.).

4·0 gm. copper bronze.

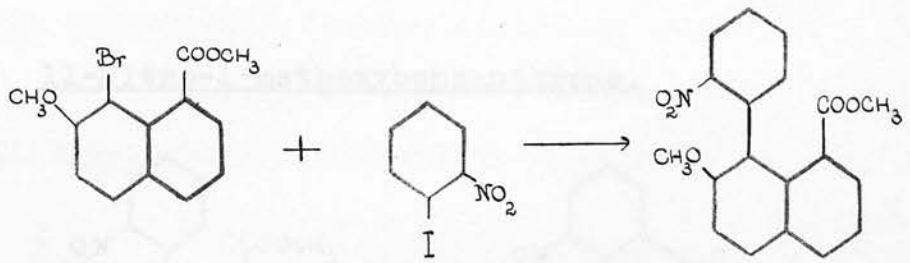
The temperature was maintained at 175°-180°C during the introduction of the copper (over a period of 45 minutes). The mixture was then stirred for four hours at 190°-200°C, the organic matter extracted with acetone, and the acetone distilled off. Ether (4 cc.) was added

to the warm oily residue, and the solution set aside at 0°C. No solid appeared in the solution even after several days. The ether was now evaporated off and the residual oil heated with concentrated sulphuric acid for one hour at 100°C. No red or green colour appeared in the solution, and on pouring into water a semi-solid dark mass was thrown out. The supernatant liquid was decanted from this mass, and the latter washed by decantation. It was then heated with alkali for a few minutes at 60°C, the alkaline solution decanted off and acidified with dilute sulphuric acid. The solid which separated was filtered off and washed with water. It weighed 3·0 gm. and proved to be, on examination, 2-chloro-3:5-dinitrobenzoic acid. The oily alkali-insoluble fraction of the reaction-product contained iodine, and weighed 2·5 gm. It was presumably unchanged 1-iodo-2-methylnaphthalene.

It was thus obvious that neither of the two substances in the above Ullmann reaction had interacted with the copper, merely being recovered unchanged from the reaction mixture.

11-Nitro-1-methoxybenzanthrone.

a) Methyl 7-methoxy-8-(o-nitrophenyl)-1-naphthoate.



6·5 gm. methyl 8-bromo-7-methoxy-1-naphthoate, (1 mol.).

5·5 gm. o-iodonitrobenzene (1 mol.).

8·0 gm. copper bronze.

The mixture of esters was heated on an oil-bath at 230°C and efficiently stirred while the copper was added in small portions over a period of one hour. After all the copper had been added the mixture was maintained with stirring at the same temperature for a further three hours. The reaction product was then boiled out with 100 cc. acetone (in four portions), and the insoluble inorganic matter filtered off. On evaporation of the acetone extract to small volume (10 cc.) crystals of methyl 7-methoxy-8-(o-nitrophenyl)-1-naphthoate separated, and were filtered off and dried.

Yield 3·5 gm. (51%). M.p. 184-185°C.

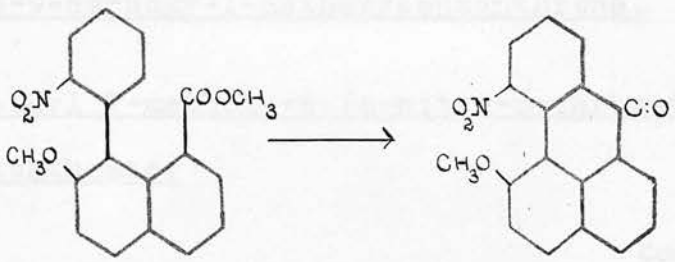
The pure phenylnaphthyl carboxylate crystallises in yellow needles from ligroin, m.p. 185°C. For conversion to 11-nitro-1-methoxybenzanthrone, however, there

is no need to purify the product.

Analysis: found, C, 68·1%, H, 4·5%, N, 4·3%:

calculated for $C_{19}H_{15}O_5N$, C, 67·7%, H, 4·5%, N, 4·2%.

b) 11-Nitro-1-methoxybenzanthrone.



3 gm. nitro-ester from a).

30 cc. concentrated sulphuric acid.

The mixture was heated with stirring at 50°C for fifteen minutes and the red solution poured into water. The green solid was filtered off, washed well with water, and dried.

Yield: 2·6 gm. (96%). M.p. 222-224°C.

Pure 11-nitro-1-methoxybenzanthrone was obtained in greenish plates on recrystallisation from glacial acetic acid. M.p. 224°-225°C.

Analysis:

found, C, 70·8%, H, 3·6%, N, 4·6%:

calculated for $C_{18}H_{11}O_4N$, C, 70·2%, H, 3·8%, N, 4·3%.

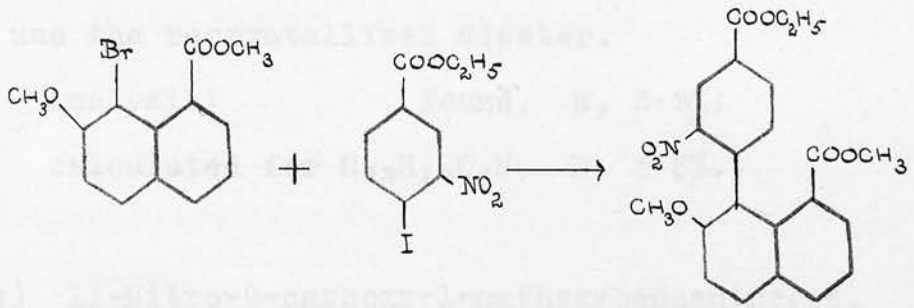
The cyclisation was also brought about by allowing the nitro-ester to stand for 50 hours in concentrated sulphur-

ic acid at room temperature.

11-Nitro-1-methoxybenzanthrone dissolves in concentrated sulphuric acid to give a red-violet solution with no appreciable fluorescence.

11-Nitro-9-carboxy-1-methoxybenzanthrone.

a) Methyl 7-methoxy-8-(o-nitro-p-carboethoxyphenyl)-1-naphthoate.



5·6 gm. methyl 8-bromo-7-methoxy-1-naphthoate. (1 mol.)

6·0 gm. ethyl 4-iodo-3-nitrobenzoate (1 mol.).

6·6 gm. copper bronze.

The mixture of esters was heated on an oil-bath at 220°C and the copper added in small portions over a period of forty-five minutes, the mixture being efficiently stirred during the addition. The temperature was then raised to 230°C and maintained at this figure for four hours, the stirring still being continued. The organic matter was then extracted with acetone in the usual manner, the acetone extract evaporated to dryness on

the steam-bath and 20 cc. ether added to the warm residual oil. After standing overnight the small crystals which separated out were filtered off, washed with a little ether, and dried.

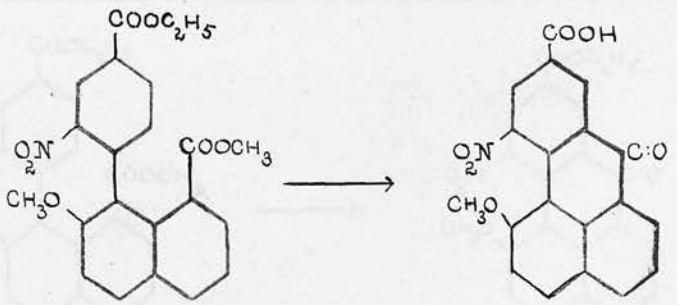
Yield: 4·8 gm. (63%). M.p. 159-162°C.

The pure phenylnaphthyl dicarboxylate crystallises from petroleum ether (b.p. 100°-120°) in stout orange prisms of melting point 163°C. For cyclisation to the benzanthrone it was found in this case more satisfactory to use the recrystallised diester.

Analysis: found, N, 3·5%;

calculated for $C_{22}H_{19}O_7N$, N, 3·5%.

b) <u>11-Nitro-9-carboxy-1-methoxybenzanthrone.</u>



3·0 gm. methyl 7-methoxy-8-(o-nitro-p-carboethoxyphenyl)-1-naphthoate.

30 cc. concentrated sulphuric acid.

The phenylnaphthyl dicarboxylic ester was heated in the sulphuric acid at 100°C for twenty minutes with stirr-

ing, and the orange-red solution poured into water. The greenish-yellow solid thrown down was filtered off, washed well with water and dried.

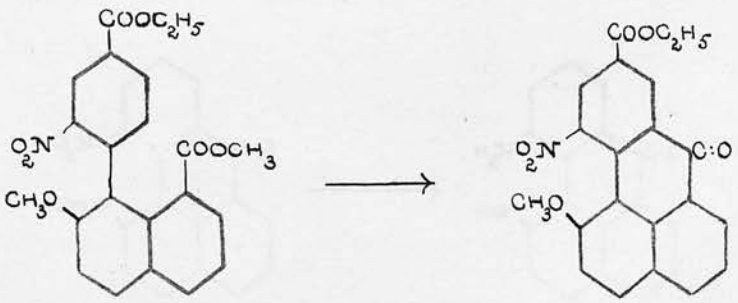
Yield: 2·5 gm. (98%). M.p. 305°-309°C (decomp.)

On crystallisation from nitrobenzene pure 11-nitro-9-carboxy-1-methoxybenzanthrone was obtained in the form of dark yellow crystals of melting point 309°-311°C (decomp.). The compound, in concentrated sulphuric acid, yields an orange-red solution without fluorescence, and dissolves in alkali to form an orange non-fluorescent solution.

Analysis: found: C, 65·1%, H, 3·4 %, N, 4·2%.

calculated for $C_{19}H_{11}O_6N$: C, 65·3%, H, 3·15%, N, 4·0%,

<u>11-Nitro-9-carboethoxy-1-methoxybenzanthrone.</u>



3·0 gm. methyl 7-methoxy-8-(o-nitro-p-carboethoxy-phenyl)-1-naphthoate.

30 cc. concentrated sulphuric acid.

The phenylnaphthyl dicarboxylic ester was dissolved in the sulphuric acid, and the solution heated with stirr-

ing at 50°C for fifteen minutes. The orange-red solution was then poured into water, and the yellow solid thrown out, filtered off, washed and dried.

Yield: 2·6 gm. (94%). M.p. 240°-243°C.

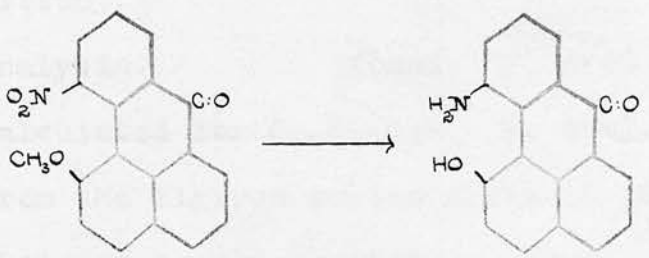
The pure phenylnaphthyl dicarboxylic ester crystallises from glacial acetic acid in orange prisms of melting point 245°C. It forms an orange-red non-fluorescent solution in concentrated sulphuric acid.

Analysis: found, N, 3·7%;

calculated for $C_{21}H_{15}O_6N$, N, 3·7%.

SOME REACTIONS OF 11-NITRO-1-METHOXYBENZANTHRONE.

I. 11-Amino-1-hydroxybenzanthrone.



2·0 gm. 11-nitro-1-methoxybenzanthrone.

40 cc. 15% sodium sulphide solution

40 cc. water.

11-Nitro-1-methoxybenzanthrone was added to the sodium sulphide solution and water. The suspension

was then brought slowly to the boiling point over a period of twenty minutes, stirring being continued throughout. The mixture was heated under reflux for two hours, during which time an intense red colour developed and the bulk of the solid went into solution. The latter was then filtered from unchanged material, the filtrate rendered neutral with dilute sulphuric acid, and the reddish-brown precipitate filtered off, washed well with cold water, and dried.

Yield: 1·8 gm. (95%). M.p. 250°-260°C (decomp.).

Owing to the extreme insolubility of this substance in the usual solvents it was found impossible to purify it by recrystallisation. It was therefore boiled out repeatedly with carbon disulphide until a reasonably sharp melting point was obtained (262°-263°C with decomposition).

Analysis: found, N, 4·8%:

calculated for $C_{17}H_{11}O_2N$, N, 5·4%.

From the figures quoted above it is probable that the substance is not completely pure. This difficulty of obtaining pure specimens of hydroxybenzanthrones has been emphasised by previous workers.

That the solubility of the compound in alkali is not due to benzanthrol formation is shown by the stability of benzanthrone itself under similar reducing conditions.

2·0 gm. benzanthrone.

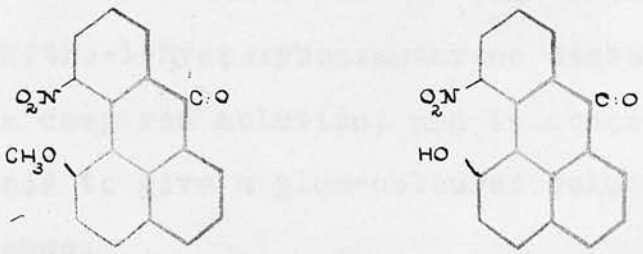
40 cc. 15% sodium sulphide solution.

40 cc. water.

The procedure was similar to that employed in the previous experiment, and although a faint pink colour was produced in the solution after two hours boiling the benzanthrone was recovered quantitatively.

11-Amino-1-hydroxybenzanthrone, in concentrated sulphuric acid, yields a reddish-purple solution with a pronounced green fluorescence and, as stated above, it dissolves in alkali to form a solution intensely red in colour.

II. <u>11-Nitro-1-hydroxybenzanthrone.</u>



2·0 gm. 11-nitro-1-methoxybenzanthrone.

50 cc. alcoholic potassium hydroxide (3%).

The above were boiled under reflux on the water-bath for two hours. During this time an intense red colour developed and the benzanthrone went into solution.

The latter was filtered from a little unchanged material, the filtrate acidified with dilute sulphuric acid and the dark green precipitate filtered off and washed with water.

Yield: 1·2 gm. (63%). M.p. >350°C.

11-Nitro-1-hydroxybenzanthrone, as in the case of 11-amino-1-hydroxybenzanthrone, could not be purified by recrystallisation. It was boiled out with carbon disulphide until no further coloration could be detected in that solvent. The benzanthrone was then boiled out several times with petroleum ether (b.p. 100°-120°C) and a brownish solid finally obtained. M.p. >350°C.

Analysis: found, N, 3·7%:

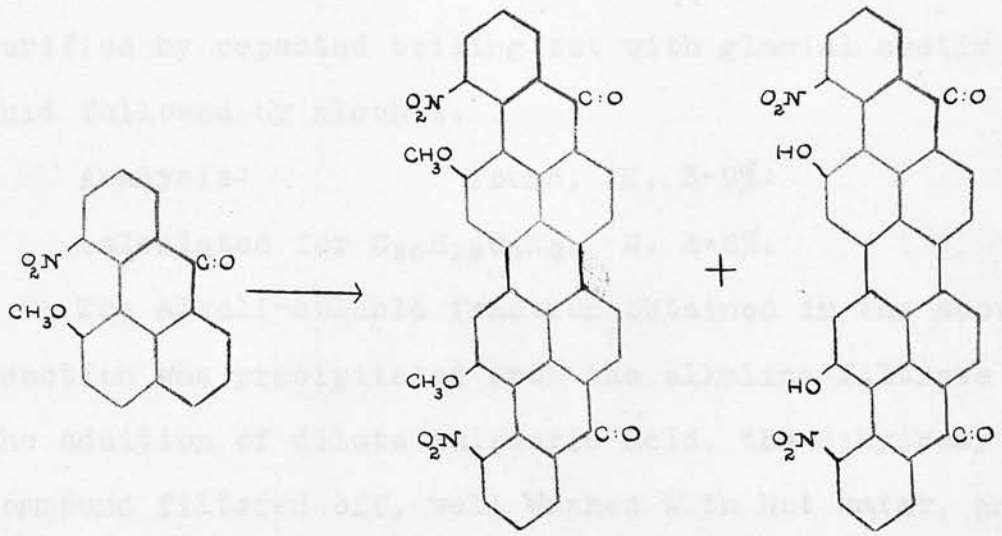
calculated for $C_{17}H_9O_4N$, N, 4·8%.

The unsatisfactory nature of these analysis figures is discussed in another part of this thesis.

11-Nitro-1-hydroxybenzanthrone dissolves in alkali to give a deep red solution, and in concentrated sulphuric acid to give a plum-coloured solution with a green fluorescence.

An attempt was made to find if the hydrolysis of the methoxyl group in 11-nitro-1-methoxybenzanthrone could be effected by the action of aqueous alkali. It was found, however, that 11-nitro-1-methoxybenzanthrone was recovered unchanged after six hours heating under reflux with 2N. caustic soda solution.

III. 11:11'-Dinitro-1:1'-dimethoxydibenzanthrone and 11:11'-dinitro-1:1'-dihydroxydibenzanthrone.



1·0 gm. 11-Nitro-1-methoxybenzanthrone.

3·2 gm. potassium hydroxide.

The alkali was placed in a small nickel tube and the latter heated in an oil-bath at 220°C. 11-Nitro-1-methoxybenzanthrone was then added in portions to the molten mass. When the addition was complete the melt was maintained at 220°C for twenty minutes and the product then boiled with 200 cc. water for a few minutes. The suspension was filtered, the alkali-insoluble fraction washed with hot water, and dried. It was then boiled with 50 cc. glacial acetic acid to remove any unchanged benzanthrone, filtered, washed with hot water, and dried.

Weight: 0·25 gm. M.p. > 350°C.

11:11'-Dinitro-1:1'-dimethoxydibenzanthrone is practically insoluble in all organic solvents and was purified by repeated boiling out with glacial acetic acid followed by alcohol.

Analysis: found, N, 3·9%:

calculated for $C_{36}H_{18}O_8N_2$, N, 4·6%.

The alkali-soluble fraction obtained in the above reaction was precipitated from the alkaline filtrate by the addition of dilute sulphuric acid, the dihydroxy compound filtered off, well washed with hot water, and dried. It was then boiled with glacial acetic acid (100 cc.) as in the previous case, filtered off and washed.

Weight: 0·65 gm. M.p. > 350°C.

11:11'-Dinitro-1:1'-dihydroxydibenzanthrone was purified in the same way as the dimethoxy compound.

Analysis: found: N, 4·0%:

calculated for $C_{34}H_{14}O_8N_2$, N, 4·8%.

11:11'-Dinitro-1:1'-dimethoxydibenzanthrone forms a violet hydrosulphite vat from which cotton is dyed a dull grey, fast towards alkali; it dissolves in concentrated sulphuric acid to yield a reddish-brown solution without fluorescence.

11:11'-Dinitro-1:1'-dihydroxydibenzanthrone gives a violet vat with alkaline hydrosulphite. Cotton

,however, is not dyed from this vat, the grey colour imparted to the fabric being quickly washed out with water. This dibenzanthrone also dissolves in concentrated sulphuric acid with a reddish-brown colour, and in alkali with a dull red colour.

Comparison of the rates of anthanthrone formation from 10:11-benzobenzanthrone-1'-carboxylic acid and the corresponding ester on treatment with concentrated sulphuric acid.

In this experiment equal weights (0·04 gm.) of 10:11-benzobenzanthrone-1'-carboxylic acid and the corresponding methyl ester were dissolved in equal volumes (5 cc.) of concentrated sulphuric acid in pyrex test-tubes, and the latter immersed in a thermostat at 50°C. The colour changes were noted at intervals. The results are tabulated below.

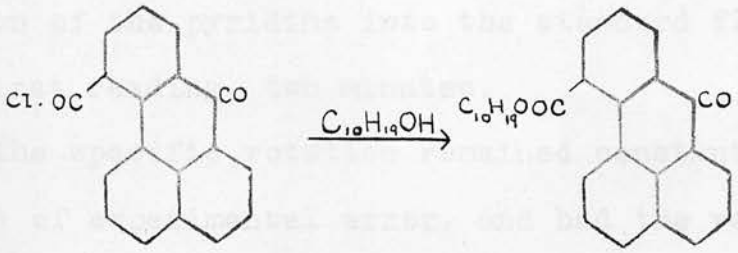
Time in minutes	Colour Changes	
	Acid	Ester
1	Intense Red	Yellow-orange
4	Faint suggestion of brown	Orange
8	Definite trace of brown	do.
13	Definately brown	do.
18	Dark brownish-green	do.
26	Greenish-brown	do.
35	Dull green	do.
48	Almost pure green	do.
60	Pure green	do.
3 days	Pure green	Pure green

The change taking place in these reactions is, in the first case, the cyclisation of 10:11-benzobenzanthrone-1'-carboxylic acid to anthanthrone, and, in the second the production of anthanthrone from the benzobenzanthrone carboxylate. The latter gives an orange solution in concentrated sulphuric acid, the acid an intense red solution, and anthanthrone a green solution.

As can be seen from the changes tabulated the formation of anthanthrone takes place much more rapidly from 10:11-benzobenzanthrone-1'-carboxylic acid than from the corresponding methyl ester.

The theoretical significance of this result is fully discussed in another part of this thesis (p. 49).

Examination of the ℓ-Menthyl Ester of 11-Carboxybenzanthrone for Mutarotation.



The ℓ-menthyl ester of 11-carboxybenzanthrone was prepared by J. L. Grieve (Thesis, Edinburgh, 1936) by the action of ℓ-menthol on the acid chloride of 11-carboxybenzanthrone. Attempts were also made by Grieve (loc. cit.) without success to resolve this compound into two stereoisomeric forms by crystallisation.

A sample of Grieve's preparation was obtained and has now been examined for mutarotation in pyridine solution.

0·1720 gm. ester was finely powdered and dissolved in 10 cc. pure pyridine in a standard flask. The solution was then quickly transferred to a 2-decimetre polarimeter tube and the rotation measured at intervals over a period of two hours.

The specific rotation, $\left[\alpha\right]^{20}_{5461}$, was calculated from the formula

$$\left[\alpha\right]^{20}_{5461} = \frac{\alpha \times 10}{w \times 2}$$

where w represents the weight of ester used.

The time taken in making up the solution of the material was one minute; from the moment of introduction of the pyridine into the standard flask until the first reading, two minutes.

The specific rotation remained constant within the limits of experimental error, and had the value -176·2°.

The Cinchonine Salt of 10:11-Benzobenzanthrone-1'-carboxylic acid.

Before the cinchonine salt of the acid was obtained attempts were made to prepare the brucine, strychnine, and quinine salts, all without success.

(I) Equivalent quantities of the benzobenzanthrone carboxylic acid and brucine were each dissolved in the minimum quantity of boiling acetone and the solutions mixed. After standing for twenty-four hours at 0°C an almost quantitative recovery of the original acid was made, confirmed by melting point and mixed melting point.

(II) A similar experiment, but using ethyl acetate as solvent, was carried out and a similar result obtained.

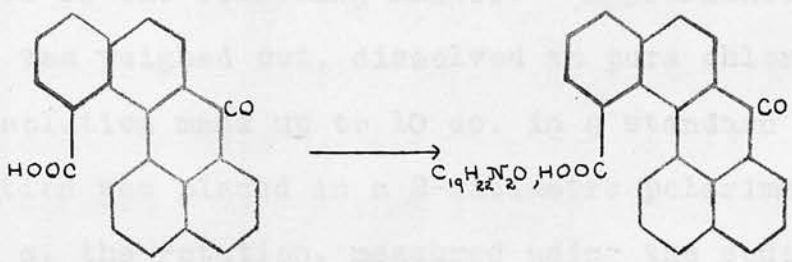
(III) Equivalent quantities of the acid and quinine were dissolved in boiling acetone and the above procedure repeated. After twenty-four hours an almost quantitative recovery of the acid and of quinine was made.

(IV) Ethyl acetate as solvent in (III) had a like result.

(V) 0·10 gm. of acid was dissolved in the minimum amount of boiling ethyl acetate and a boiling solution of strychnine (0·10 gm. in 100 cc.) added. A slight residue was filtered off and the filtrate allowed to stand for some days at 0°C. A very fine precipitate settled out (0·09 gm.) which, on examination, proved to be the original acid.

These experiments were all repeated but in no case was there any trace of the alkaloidal salt being formed.

(VI)



1·40 gm. 10:11-benzobenzanthrone-1'-carboxylic acid
1·28 gm. cinchonine.

The cinchonine and benzobenzanthrone carboxylic acid were each dissolved in the minimum amount of boiling ethyl acetate, the solutions mixed, and boiled for two minutes. A slight residue was filtered off and the filtrate set aside at 0°C for twenty-four hours. Small

prismatic crystals, of an orange-yellow colour, were deposited, and were filtered off and dried.

Yield: 1·60 gm. (60%). M.p. 183-185°C.

This melting point did not change on recrystallisation.

Analysis: found, N, 3·4%:

calculated for $C_{41}H_{34}O_4N_2$, N, 3·4%.

Attempted Resolution of the Cinchonine Salt of 10:11-Benzobenzanthrone-1'-carboxylic acid.

The specific rotation of the cinchonine salt was determined in the following manner. Approximately 0·1 gm. salt was weighed out, dissolved in pure chloroform, and the solution made up to 10 cc. in a standard flask. The solution was placed in a 2-decimetre polarimeter tube and α, the rotation, measured using the sodium D line (5893A.U.). The specific rotation was given by the following formula, w representing the weight of brucine salt used.

$$[\alpha]_D = \frac{\alpha \times 10}{w \times 2}$$

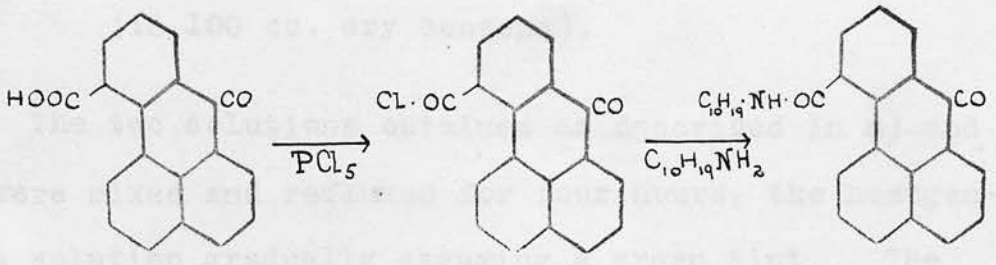
From this it was found that the original product, which crystallised from ethyl acetate, gave the specific rotation -62·7°.

The bulk of the salt (0·8 gm.) was crystallised repeatedly from absolute alcohol in each case, the rotation being taken after each recrystallisation. The product taken after four recrystallisations weighed 0·2 gm. The rotation remained practically constant throughout, varying only between the limits of experimental error, namely between -62·0° and -63·0°.

Examination of the Cinchonine Salt for Mutarotation.

A portion of the salt (0·1 gm.), which had been four times recrystallised from alcohol, was placed in a small standard flask, dissolved in pure pyridine, and the solution was made up to 10 cc. with that solvent. It was immediately transferred to a polarimeter tube and the rotation examined at intervals over two hours. The specific rotation, + 26° (5893 A.U.), remained constant during that time.

11-Carboxybenzanthrone-ℓ-menthylamide.



a) Preparation of a solution of ℓ-menthylamine.

4 gm. pure ℓ-menthylamine-ℓ-tartrate was available. This was dissolved in the minimum amount of cold water and the solution made alkaline with dilute caustic soda (2N.). The liberated base was extracted with benzene and the benzene extract dried over anhydrous sodium sulphate. The benzene solution, containing by calculation approximately 3 gm. ℓ-menthylamine, was used in the preparation of the amide without further treatment.

b) Preparation of the acid chloride of 11-carboxybenzanthrone.

5 gm. 11-carboxybenzanthrone was converted to the acid chloride in the usual manner and the latter dissolved in 100 cc. dry benzene.

c) 11-Carboxybenzanthrone-ℓ-menthylamide.

3 gm. ℓ-menthylamine (in 50 cc. dry benzene)
5 gm. acid chloride of 11-carboxybenzanthrone (in 100 cc. dry benzene).

The two solutions obtained as described in a) and b) were mixed and refluxed for four hours, the homogeneous solution gradually assuming a green tint. The solution was washed with alkali to remove any free acid,

and then with dilute sulphuric acid to remove any unchanged menthylamine. After a final washing with water the benzene solution of the amide was dried over anhydrous sodium sulphate and evaporated to dryness at room temperature. The amide separated in the form of a light yellow powder.

Yield: 7·3 gm. (97%).

The crude amide melted at 195°-202°C with a previous sintering and partial melting at 79°-100°C.

It was found that the amide, although easily soluble in benzene, and sparingly soluble in petroleum ether (b.p. 60-80° or 80-100°), could not be cleanly recrystallised from mixtures of these solvents. Indeed, no solvent for satisfactory recrystallisation could be found. The compound was finally purified by selective adsorption on anhydrous aluminium oxide, the details being given in that section of the thesis dealing with chromatographic adsorption.

M.p. 214°-216°C (with previous sintering at 98°-103°C).

Analysis: found, N, 3·1%:

calculated for $C_{28}H_{29}O_2N$, N, 3·4%.

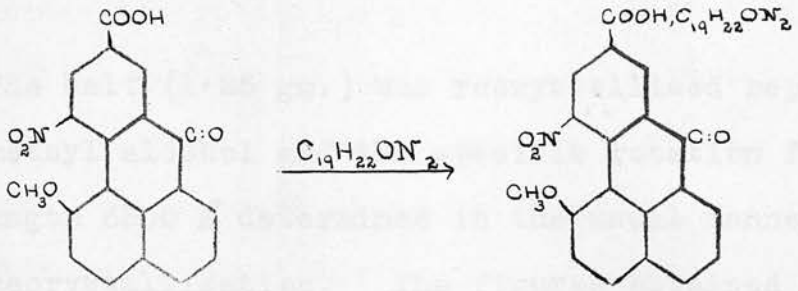
Examination of 11-carboxybenzanthrone-ℓ-menthylamide for mutarotation.

11-Carboxybenzanthrone-ℓ-menthylamide is readily soluble in benzene and rotations in this solvent were taken. Approximately 0·1 gm. amide was weighed out, dissolved quickly in pure dry benzene, and the solution made up to 10 cc. in a standard flask. Using a 2-decimetre polarimeter tube no mutarotation was observed, the variation in readings being all within the experimental error. The specific rotation remained constant and had the value -68·8° (λ 5461 and 20°C).

The Cinchonine Salt of 11-Nitro-9-carboxy-1-methoxy-benzanthrone.

Before the cinchonine salt of 11-nitro-9-carboxy-1-methoxy-benzanthrone was obtained an attempt was made to prepare the brucine salt by dissolving equivalent amounts of the acid and base in n-propyl alcohol, mixing the solutions at the boiling point, and then allowing the mixture to stand for some time at room temperature. No crystalline product, however, could be obtained from the alcoholic solution, the greater part of the benzanthrone being recovered unchanged.

Cinchonine Salt.



0·700 gm. 11-Nitro-9-carboxy-1-methoxybenzanthrone

0·602 gm. cinchonine.

The benzanthrone carboxylic acid was suspended in 250 cc. of boiling n-propyl alcohol and a boiling solution of the cinchonine in 20 cc. n-propyl alcohol added. The benzanthrone carboxylic acid went immediately into solution, a deep red colour being produced. The solution was then boiled for ten minutes, filtered from a very slight residue, and the filtrate evaporated almost to dryness on the steam-bath. Ether (20 cc.) was added to the residue, and the brownish-yellow solid filtered off, washed with a little ether, and dried.

Weight: 1·25 gm. M.p. 205-209°C. (decomp.)

The cinchonine salt of 11-nitro-9-carboxy-1-methoxy-benzanthrone crystallises from aqueous methyl alcohol in small gleaming plates of a brownish tint.

M.p. 214-215°C (decomp.).

Analysis: found, N, 6·2%:

calculated for $C_{38}H_{33}O_8N_3$, N, 6·5%.

Attempted Resolution of the Cinchonine Salt.

The salt (1·25 gm.) was recrystallised repeatedly from methyl alcohol and the specific rotation for the wavelength 6300 Å determined in the usual manner at each recrystallisation. The figures obtained showed a regular decrease from +136° to +109° (+136°, +125°, +112°, +109°). The melting point also exhibited a regular change, dropping at first from 205°C - 209°C for the crude salt and then rising to a steady value at 214°-215°C. After four recrystallisations neither the melting point or the specific rotation showed any further change. The weight of the salt had then decreased to 0·045 gm.

An equal volume of water was added to the filtrate from each recrystallisation, a further crop of crystals obtained, and specific rotation of these determined. It was found, however, that the values obtained in each case were, within the limits of experimental error, the same as these got for the corresponding crops from the pure methyl alcohol.

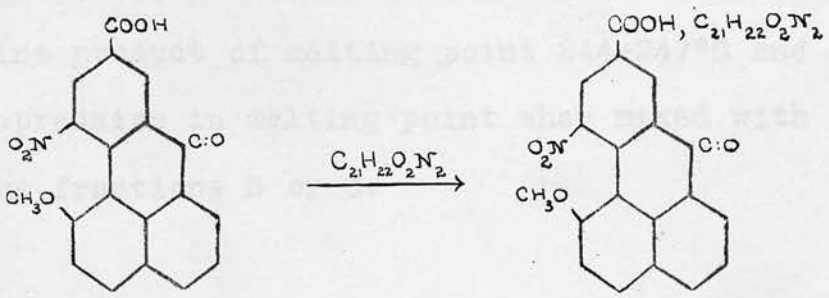
A portion of the final product was hydrolysed by warming gently for a few minutes with dilute hydrochloric acid, filtering off the free acid liberated, and washing it repeatedly with water. It melted at 308° - 310°C. and gave no rotation in alkaline solution. The insolubility

of the compound in the usual solvents made it necessary to examine it here in the form of the sodium salt.

Another portion of the final salt product was examined for mutarotation, being quickly dissolved in pure pyridine in a standard flask and transferred to a 2-decimetre polarimeter tube. The rotation remained constant within the limits of experimental error over a period of two hours, and had the value +20·2° (λ 6300 Å at 20°C.).

The results obtained above, which are fully discussed in another part of this thesis, suggested that some resolution had taken place although the complete non-activity of the free acid itself and the failure to observe any mutarotation in the salt appeared anomalous. It was decided therefore to prepare, if possible, another alkaloidal salt of 11-nitro-9-carboxy-1-methoxybenzanthrone and examine it in the same way. It was found that the strychnine salt of the benzanthrone carboxylic acid could be prepared comparatively easily.

<u>The Preparation and Examination of the Strychnine Salt of 11-Nitro-9-carboxy-1-methoxybenzanthrone.</u>



1·82 gm. 11-nitro-9-carboxy-1-methoxybenzanthrone.

1·74 gm. strychnine.

The benzanthrone carboxylic acid was suspended in 100 cc. boiling amyl alcohol and the strychnine, dissolved in 100 cc. boiling amyl alcohol, added. The mixture was heated under reflux for thirty minutes, by which time the solid acid had gone almost completely into solution, an intense red colour developing. The solution was now filtered, and allowed to stand overnight. The brownish-red micro-crystalline product which separated was filtered off. (A).

Weight: 1·90 gm. M.p. 165°-170°C.

Absolute alcohol (200 cc.) was added to the filtrate and the latter again set aside for twenty-four hours. The crop of orange-yellow prisms which separated was filtered off. (B).

Weight: 0·50 gm. M.p. 245°-248°C.

On addition of a further 200 cc. absolute alcohol to the filtrate from B a third crop of crystals of the strychnine salt was obtained. (C).

Weight: 0·25 gm. M.p. 244°-247°C.

Fraction A on recrystallisation from amyl alcohol (three times) is obtained in the form of a micro-crystalline product of melting point 244-247°C and suffers no depression in melting point when mixed with either of the fractions B or C.

Analysis: found, N, 5·9%;

calculated for $C_{40}H_{33}O_8N_3$, N, 6·2%.

The specific rotations of the fractions A, B, and C were examined separately.

A. It was found that the degree of colour possessed by this fraction rendered any attempt to determine its specific rotation of little value, the maximum concentrations practicable giving almost negligible rotations. Even on repeated crystallisation from amyl alcohol and treatment with animal charcoal the colour did not lessen in intensity. The melting point, however, gradually rose and ultimately attained constant value at 244°-247°C. A portion of this final product was hydrolysed by vigorously shaking it with dilute hydrochloric acid, the free benzanthrone carboxylic acid filtered off and washed. The latter was examined, in the form of the sodium salt, in the polarimeter but was found to be completely inactive.

B. This fraction, melting at 245°-248°C, gave a specific rotation, at λ6300 Å and 20°C, of +14·3° and on one recrystallisation from amyl alcohol - absolute alcohol (1:1) yielded a product of the same melting point but having a specific rotation, under the same conditions, of +7·1°.

C. The specific rotation of this fraction was +6·6°. This figure being, within the limits of experimental error, the same as that obtained from the recrystallised product of B, and the melting points being the same, these two latter were mixed. On recrystallisation from the amyl alcohol - absolute alcohol mixture a crop of crystals of melting point 246°-248°C and of specific rotation +7·0° was obtained.

Since the specific rotation and melting point of the mixed fraction B and C had apparently attained constant values a portion of this final product was hydrolysed and the sodium salt of the free acid examined. It gave, however, no rotation.

Another portion was dissolved in pyridine, made up to 10 cc. in a standard flask, and quickly transferred to a 2-decimetre polarimeter tube. The rotation did not vary outside the limits of experimental error over a period of two hours and had the value -50·0° (λ6300 Å at 20°C).

The theoretical significance of the above results is discussed on page 56 et seq.

CHROMATOGRAPHIC ADSORPTION.

General Experimental Procedure.

The purification and separation of substances by chromatographic adsorption methods relies, in general, on a well-defined technique. The process may be divided into three stages: a), adsorption; b), development; and c), elution.

a) The substance in solution is allowed to run through a tube filled with a suitable adsorbent.

b) The adsorbed matter is spread and separated into bands by running a selected pure solvent through the tube.

c) The bands which form, and which are differentiated by their colour, or if colourless, by their fluorescence in ultra-violet light, are separated and the adsorbed material "eluted" by treatment of the adsorbent and its adsorbate with a suitable solvent.

Theoretical considerations and fuller details of the process are given in another part of this thesis (page 62).

The Purification of 11-Carboxybenzanthrone-ℓ-menthylamide.

As stated on page 66 11-carboxybenzanthrone-ℓ-menthylamide could not be purified by recrystallisation and resort was made to chromatographic adsorption methods.

2·0 gm. crude amide was dissolved in 200 cc. cold dry benzene (A.R.) and this solution allowed to flow, at the rate of one drop per second, through a glass tube containing specially prepared aluminium oxide.

At the lower end of a glass tube thirty inches in length and 16 mm. bore a tap was attached by which the flow of liquid through the tube could be adjusted. A paste consisting of anhydrous aluminium oxide (prepared and marketed by Merck, Darmstadt, for the purpose) and benzene was then run into the tube, and the benzene run slowly off until the supernatant liquid almost reached the level of the oxide. The diagram opposite shows the prepared adsorption tube.

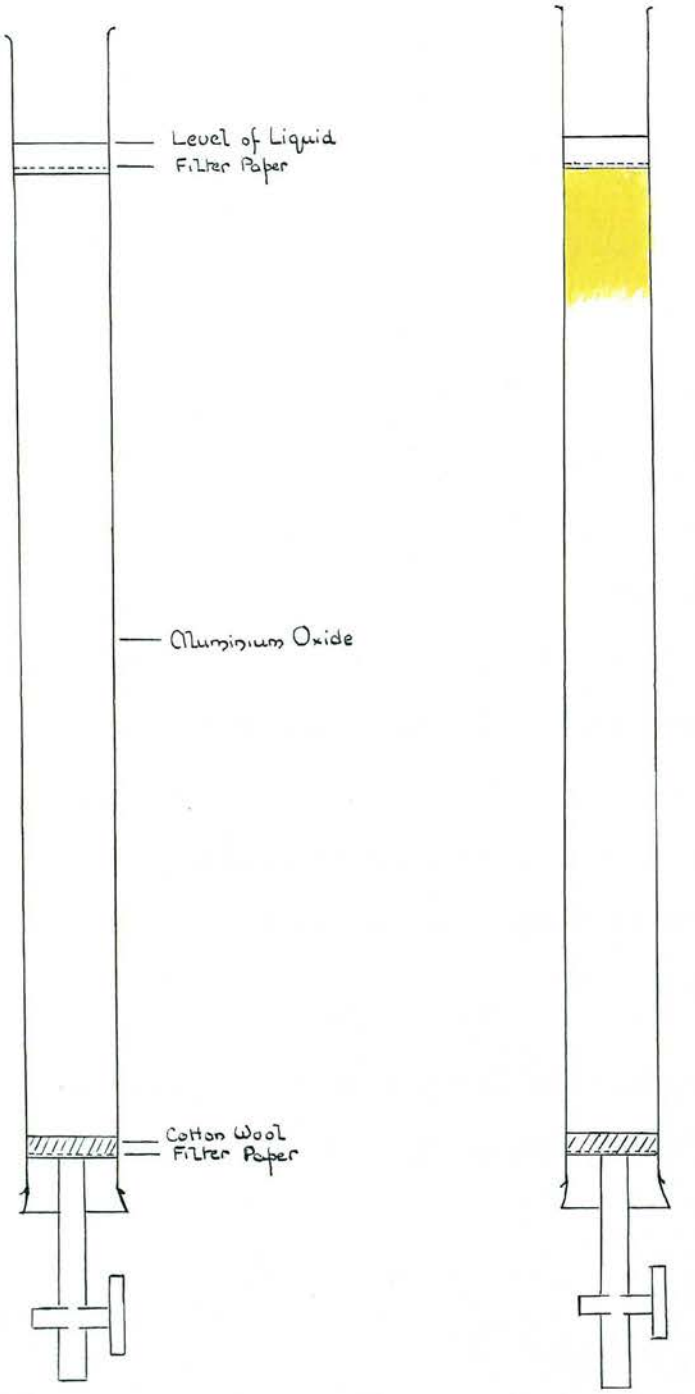
The amide solution was then allowed to flow through the tube at the rate of one drop per second, and pronounced adsorption took place as was indicated by the appearance of a narrow yellow band at the top of the aluminium oxide column. (STAGE I in diagram)

When all the amide solution had been poured into the tube, and had reached the level of the top of the

ADSORPTION OF 11-CARBOXYBENZANTHRONE-ℓ-MENTHYLAMIDE ON ALUMINIUM OXIDE

Prepared Adsorption Tube

(this type of adsorption tube was used throughout the course of the present work.)



Stage I

ADSORPTION OF 11-CARBOXYBENZANTHRONE-ℓ-MENTHYLAMIDE ON ALUMINIUM OXIDE



Stage II

oxide column, 100 cc. of dry benzene was run through. The yellow band widened on this treatment. Although only one band could be seen by the eye the appearance of the tube, under ultra-violet light, indicated that in addition to the main yellow band there were two others due to the presence of impurities. These bands only became apparent when irradiated with ultra-violet light when they exhibited strong fluorescence. The diagram appended (STAGE II page 149A) shows the appearance of the tube at this stage.

The pure amide was located in band A, while in bands B and C were adsorbed small amounts of impurities.

The tube was now cut at α and β, the aluminium oxide between these limits removed, and the amide obtained by treatment of the aluminium oxide with acetone. The acetone extract was filtered from the oxide and evaporated to dryness, yielding 1·4 gm. of pale yellow crystals.

M.p. 214°-216°C (with previous sintering at 98°-103°C).

The melting point of the crude amide was 195°-202°C with previous sintering and partial melting at 79° - 100°C.

The purified amide was submitted to a further adsorption under the same conditions but no further purification was effected, the melting point remaining unchanged.

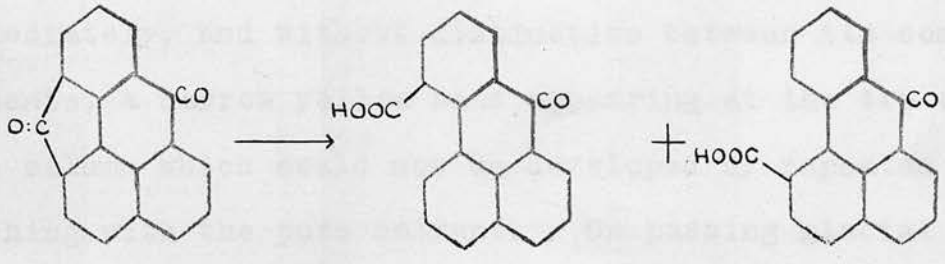
Attempted separation of the acid mixture obtained by the hydrolysis of 1:11-ketobenzanthrone.

1:11-Ketobenzanthrone, on alkaline hydrolysis, yields a mixture of 1-carboxybenzanthrone and 11-carboxybenzanthrone. Attempts to separate this mixture into its components by fractional crystallisation have failed (Rule and Bigelow, unpublished).

The partial esterification of the acid mixture was carried out by J. L. Grieve, (Thesis, Edinburgh, 1936) and the esterified portion crystallised repeatedly. A very small amount of the ester of 11-carboxybenzanthrone was all that was finally obtained by this treatment.

The success which attended the purification of 11-carboxybenzanthrone-ℓ-menthylamide by the adsorption method led to its employment in an attempted separation of the acid mixture.

Hydrolysis of 1:11-Ketobenzanthrone.



1:11-Ketobenzanthrone (6·5 gm.) was dissolved in

concentrated sulphuric acid (20 cc.) by warming, the solution poured into water and the finely divided solid filtered off. It was added to 750 cc. dilute sodium hydroxide solution (10%) and the mixture boiled under reflux. The solid gradually dissolved to give a red solution, hydrolysis being complete after eight hours. The solution was filtered from a slight residue and the filtrate acidified to give an orange-yellow precipitate of the mixed acids. It was filtered off, washed with water and dried.

Yield: 6·0 gm. M.p. 220°-240°C.

Attempted separation of the acid mixture by adsorption methods.

I). The acid mixture (0·20 gm.) was dissolved in 100 cc. acetone and the solution filtered from a slight residue. It was then run through an adsorption tube (16 mm. bore) packed with aluminium oxide.

The mixture was apparently adsorbed by the oxide immediately, and without distinction between its components, a narrow yellow band appearing at the top of the column which could not be developed by repeated washing with the pure solvent. On passing glacial acetic acid down the tube, however, this yellow band was displaced completely, carried down the tube, and

gave a yellow solution in the glacial acetic acid. The solution was collected, an excess of water added to it, and the yellow substance which separated filtered off, washed and dried.

Yield: 0·15 gm. M.p. 220-240°C.

It was concluded from this experiment that traces of water in the acetone, and from which it could not be completely freed, were forming, with the aluminium oxide, the basic hydroxide, and that this base was then combining with the acid mixture to form aluminium salts. This supposition would explain the complete non-development of the primary band on washing with acetone. On treatment with glacial acetic acid, however, the metallic radical of the salt would presumably be displaced, the original acids formed and washed through the tube. No separation, in any case, was effected.

II). An attempt was made to overcome the difficulties encountered in the previous experiment by using lactose as an adsorbent. The lactose was dried in vacuo at 100°C and finely powdered. It was packed into a tube (16 mm. bore) in the usual manner and a 0·2% solution of the mixed acids in acetone run through. No adsorption, however, took place, the original material being recovered quantitatively from the solution collected at the foot of the adsorption tube.

The acidity of the acid mixture, and its sparing solubility in organic solvents at ordinary temperatures, are both factors which produce complications in adsorption work. The esters of the acids, however, suffer from neither of these disadvantages and were therefore employed in another attempt at separation.

Esterification of the acid mixture.

5·0 gm. mixed acids
6·5 gm. purified phosphorus pentachloride
150 cc. dry benzene
50 cc. absolute alcohol.

The mixed acids were converted to the acid chlorides as described in the preparation of the acid chloride of 11-carboxybenzanthrone. Alcohol was then added to the greenish-yellow residue and the solution heated under reflux for two hours. The bulk of the alcohol was then evaporated off on the water-bath and dilute caustic soda solution (2N.) added. After warming to 60°C for a few minutes the alkali-insoluble mixed esters were filtered off, washed with hot water and dried.

Yield: 5·0 gm. M.p. 109°-145°C (with slight sintering at 81°C.)

Attempted separation of the ester mixture by adsorption methods.

The mixed esters (5·0 gm.) were dissolved in 250 cc. dry benzene (A.R.) and the solution passed, at the rate of one drop per second, down a tube packed with anhydrous aluminium oxide. Adsorption took place and was indicated by the appearance of an orange-yellow band at the top of the column. This band, on development with 150 cc. benzene, was spread over a length of twenty inches, the top half being an orange-yellow colour, the bottom a pure yellow colour.

The band was cut in two halves and the adsorbed material on each half eluted by heating with 250 cc. absolute alcohol (in three portions). The alcoholic solution of the esters was filtered from the oxide and evaporated to dryness, the residue from the top part of the band (A) being orange-yellow, from the bottom part (B) pure yellow.

A. yield: 0·80 gm.

M.p. 116°-141°C. (slight sintering at 112°C.)

B. yield: 3·00 gm.

M.p. 111°-140°C. (slight sintering at 91°C.)

The above adsorption process was now repeated sep-

arately with the fractions A and B, 2% solutions in benzene being used. The adsorption bands were divided into two sections as before, the adsorbed material eluted with alcohol, and the melting points examined.

The top part of the band obtained from the fraction A (C) was coloured orange, and the bottom part of the band obtained from the fraction B (D) yellow.

C. yield: 0·15 gm.
M.p. 111°-132°C. (slight sintering at 95°C.)

D. yield: 1·20 gm.
M.p. 136°-150°C. (slight sintering at 104°C.)

The fraction C was again submitted to the usual adsorption process, the top fraction (E) collected and examined as before. It was deep orange in colour.

E. yield: 0·03 gm.
M.p. 95°-180°C. (slight sintering at 65°C.)

The fraction D, on two crystallisations from ethyl alcohol, gave 0·75 gm. of a pale yellow compound melting sharply at 159°C and showed no depression in melting point when mixed with a pure specimen of ethyl benzanthrone-11-carboxylate.

The table below summarises and clarifies the above operations.

Mixture of ethyl benzanthrone-1-carboxylate and ethyl benzanthrone-11-carboxylate

5·0 gms.

1st Adsorption

A Upper Part — Lower Part B

0·80 gm. — 3·0 gm.

M.p. 116°-141°C (sinters at 112°C) — M.p. 111°-140°C (sinters at 91°C)

2nd Adsorption

C Upper Part — Lower Part — Upper Part — Lower Part D

0·15 gm. — 0·42 gm. — 0·90 gm. — 1·20 gm.

M.p. 111°-132°C (sinters at 95°C) — M.p. 136°-150°C (sinters at 104°C)

3rd Adsorption

recrystallised from ethyl alcohol

E Upper Part — Lower Part

0·03 gm. — 0·05 gm.

M.p. 95°-180°C (sinters at 65°C)

Pure ethyl benzanthrone-11-carboxylate

Yield: 0·75 gm.

M.p. 159°C.

By this process 0·75 gm. of pure ethyl benzanthrone 11-carboxylate was obtained from 5·0 gm. of the mixture of ethyl benzanthrone-11-carboxylate and ethyl benzanthrone-1-carboxylate. Ethyl benzanthrone-11-carboxylate, which is yellow in colour, from the figures above evidently constitutes the main bulk of the mixture. The orange-coloured fraction obtained in the adsorption did not become purer on repeated treatment, the melting point exhibiting a greater range after each operation, and the colour undergoing a parallel intensification. This rather peculiar behaviour may be due to the concentration of a highly-coloured high melting impurity which is adsorbed with ethyl benzanthrone-1-carboxylate. The matter is discussed more fully in another part of this thesis.

The Purification of Dimethyl x:x'-dinitro-1:1'-dinaphthyl -2:2'-dicarboxylate.

Dimethyl x:x'-dinitro-1:1'-dinaphthyl-2:2'-dicarboxylate is prepared by treating methyl 1-bromo-x-nitro-2-naphthoate with copper bronze at 200°C, and is obtained as a dark brown powder difficult to purify by ordinary means. It melts, in the crude state, over the range 226°-236°C.

This crude product, in 2% acetone solution, was passed down a tube packed with anhydrous aluminium oxide and adsorption of a dark brown substance was observed on the upper part of the oxide. After all the acetone solution had passed through the tube an equal volume of pure acetone was passed through. There was no movement of the adsorbed material on this treatment but the filtrate from the tube was coloured orange. This filtrate was collected, the acetone evaporated off, and a light brown residue obtained.

Yield: 80%. M.p. 233°-240°C.

From consideration of the melting point range of the dinaphthyl dicarboxylate before and after adsorption treatment it might appear that no great purification had been effected. It was found, however, that the product could now be quickly and cleanly recrystallised from glacial acetic acid to give the pure dimethyl x:x'-dinitro-1:1'-dinaphthyl-2:2'-dicarboxylate.

M.p. 250°C.

The Purification of Dimethyl $x:x_1:x':x_1'$etetranitro-1:1'-dinaphthyl-2:2'-dicarboxylate.

The purification of dimethyl $x:x_1:x':x_1'$-tetranitro-1:1'-dinaphthyl-2:2'-dicarboxylate, prepared by the action of copper bronze on methyl 1-bromo-$x:x_1$-

dinitro-2-naphthoate, was carried out in the same manner as described in the previous case. A 2% solution of the dinaphthyl dicarboxylate in acetone was run through a tube packed with aluminium oxide, the product collected, the acetone evaporated off, and the residue examined.

A small amount of a dark-coloured substance remained adsorbed on the oxide. The melting point of the original crude material was 260°-270°C and of the material purified by adsorption of impurities, 307-312°C. The yield was 84%.

On recrystallisation of the clarified product from glacial acetic acid (twice) brownish plates of pure dimethyl $x:x_1:x':x_1'$-tetranitro-1:1'-dinaphthyl-2:2'-dicarboxylate were obtained.

M.p. 333°-334°C.

S U M M A R Y.

Various attempts have been made to synthesise 1:11-disubstituted benzanthrones and some interesting results have been obtained. In an attempted synthesis of the nitrile of benzanthronylglyoxylic acid by the standard method of treating the acid chloride of 11-carboxybenzanthrone with hydrogen cyanide and pyridine the hitherto-unknown anhydride of 11-carboxybenzanthrone has been prepared. The latter has also been formed by the action of mercuric cyanide on the acid chloride. The structure has been confirmed by chemical methods and a tentative explanation of its formation in the above reactions given. The new ethyl benzanthrone-11-carboxylate has been synthesised in the course of this work.

The possibility of the utilisation of the Ullmann reaction in the synthesis of 1:11-disubstituted benzanthrones has been explored. It is concluded that 1:2-disubstituted naphthalene compounds such as methyl 1-bromo-2-naphthoate and 1-iodo-2-methylnaphthalene are of little practical use in the formation of phenylnaphthyl derivatives of the required type while 1:8-disubstituted naphthalene compounds can, in a number of cases,

be utilised very successfully in the Ullmann reaction. Employing methyl 8-bromo-7-methoxy-1-naphthoate as one of the components in the Ullmann reaction, two new phenylnaphthyl derivatives, methyl 7-methoxy-8-(o-nitrophenyl)-1-naphthoate and methyl 7-methoxy-8-(o-nitro-p-carboethoxyphenyl)-1-naphthoate, have been synthesised and, from these, two 1:11-disubstituted benzanthrones, 11-nitro-1-methoxybenzanthrone and 11-nitro-9-carboxy-1-methoxybenzanthrone, prepared. By using milder conditions of cyclisation than needed to produce the latter benzanthrone, the corresponding ester, 11-nitro-9-carboethoxy-1-methoxybenzanthrone, has been obtained. Several naphthalene derivatives not listed in the literature have been synthesised in the course of the present work and improved methods for the preparation of some halogeno-compounds worked out.

It has been concluded that a primary condition determining the capacity of a halogeno-naphthalene derivative to interact with a halogeno-benzene derivative in the Ullmann reaction to give compounds of the type under consideration lies in the 1:8-substituted character of the naphthalene molecule. It has also been shown that, in all probability, this characteristic does not depend on the activation of the halogen by the peri-substituting group alone. The empirical nature of work of this kind has been emphasised.

An examination of the 1:11-disubstituted benzanthrones synthesised has proved that they exhibit abnormalities in their reactions due to the close spatial proximity of the substituting groups. It has been demonstrated that the methoxyl group in 11-nitro-1-methoxybenzanthrone is hydrolysed under conditions which normally would leave such a grouping unaffected.

Confirmation has also been supplied to the hypothesis of Rule and Smith (J., 1937, 1099) that, in the formation of anthanthrone by a dinaphthyl dicarboxylic ester by use of sulphuric acid, the red solution contains a benzobenzanthrone carboxylic ester and not, as Kalb stated, (Ber., 1914, 47, 1724), a benzobenzanthrone carboxylic acid.

The possibility of optical isomerism occurring in 1:11-disubstituted benzanthrones due to the disposition of the closely adjacent substituting groups has been investigated, attempts having been made to resolve 10:11-benzobenzanthrone-1'-carboxylic acid, 11-carboxybenzanthrone-ℓ-menthylamide and 11-nitro-9-carboxy-1-methoxybenzanthrone. No definite resolution of any of these has been effected although, in the strychnine and cinchonine salts of the last-named, some slight evidence of activity appears to have been detected. In the case of the parent acid itself, however, it has been concluded that optically active forms are incapable of existence. A tentative explanation of this has been advanced but it

is pointed out that negative results in work of this nature are essentially provisional and that further research upon this point is required.

It has been demonstrated that the utilisation of chromatographic adsorption methods in the purification and separation of benzanthrone derivatives and allied compounds gives very satisfactory results. 11-Carboxybenzanthrone-ℓ-menthylamide has been purified readily by this method where the normal methods failed; ethyl benzanthrone-11-carboxylate has been isolated from the esterified mixture produced in the alkaline hydrolysis of 1:11-ketobenzanthrone in quotable yield where fractional crystallisation of the mixture has previously failed, and two new compounds of the dinaphthyl type have been initially purified with greater facility than would have been the case had the usual methods been employed.

In conclusion the author desires to record his gratitude to Dr. H. G. Rule for his guidance and for the interest he displayed throughout the course of the work. Thanks must also be rendered to the Carnegie Trust for the grant of a Research Scholarship.