The Synthesis of Tumour-inhibiting Compounds.

Part I. Synthesis of (2':1'-Naphtha)-2:3-fluorene and of (1':2'-Naphtha)-1:2-fluorene.

Part II. Synthesis of $\alpha\beta$ -Diarylethylenes.

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Degree of
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by
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Preface.

The author wishes to express her thanks to Professor J.W. Cook, F.R.S. for much valuable advice given throughout his supervision of the work reported here.

The author also wishes to thank the Finney-Howell Research Foundation and the International Federation of University Women for Fellowships. She is indebted to Mr. J.M. L.Cameron and Miss Kennaway for the micro-analyses.

Contents.

General Introduction.

At the present time the accepted methods for the treatment of cancer are limited almost exclusively to complete removal of the malignant tissue by surgical means or destruction of the malignant cells in situ by X-rays, or frequently to a combination of both methods. "Each of these methods has its recognised limitations, and whether or not they have nearly been reached, there would clearly be immense advantages ... since dissemination is an outstanding feature of the disease ... in any less local or more systemic control of malignant growth, such as could presumably be achieved by chemical means alone."[72a] In fact, attempts to cure cancer by the use of a wide variety of chemical agents have been known for many centuries. Thus arsenic, lead, mercury, silver, zinc, antimony and sulphur (either as the free elements or in the form of various compounds) have been widely used at different times. A great many extracts of plants and various human and animal organs have also been tried, but no successful treatment of the disease has emerged from all these trials.

With the successful development of the sciences of bacteriology and immunology towards the end of the last century it was natural that the possibility of inducing an immunity to malignant growth should be explored as well as the role of

microorganisms as causal agents for cancer. Although the results of these investigations as a whole have been disappointing, a few interesting observations have been made. For instance, it was noted many years ago that patients with advanced malignancy (more particularly carcinomas) occasionally recovered from the disease after an acute bacterial infection (more usually erysipelas). W. Coley[73] studied this and showed that the toxins of S. erysipelatis were responsible. Later work showed that B. prodigiosus formed more effective toxins. Various preparations of these toxins have been made differing in their therapeutic effects.[74] Shear and his collaborators have found that the active fraction of these toxins contains a substance of the nature of a polysaccharide having a nitrogen content of about 2%. Trials with mice have shown that doses sufficient to effect cure cause a large percentage of deaths. However, those mice which recovered from the treatment usually remained free from tumours after the regression of the original tumour. Some cases of human cancer have been treated but the results show that the toxin is not a "cure" for cancer. Nevertheless it does destroy some cancer cells before they develop an immunity to it.

Another attempt at toxin therapy has recently been made by Roskin[111] who found that some bacterial toxins and protozoan

endotoxins in adequate doses inhibit the development of certain experimental tumours in animals and cause complete regression of others. The endotoxin from Schizotrypanum cruzi was tried on several patients with incurable cancer of the pharynx with results sufficiently good to encourage further trials.

Attracted by the well known effect of the alkaloid colchicine on cell mitosis, attempts have been made to prepare substances modelled on Windaus' formula(i) for colchicine[75,77] in the hope that some of them may not only retain its anti-mitotic activity but possess a more selective action on the malignant cells than does colchicine, and be in addition less toxic to the organism. The results with the compounds so far prepared have not been encouraging. Since the structure of the colchicine is still in doubt[78], the preparation of closely related compounds cannot yet be attempted with certainty.

A number of compounds besides colchicine affect cell mitosis. For instance Lefevre[95] has reported that phenylurethane (XVII) causes mitotic effects exactly of the same nature of those of colchicine. Templeman and Sexton[97] found that ethylphenylcarbamate (XVIII) arrested the growth of cereals at lower concentrations than did colchicine. The first of these observations led Haddow and Sexton[98] to examine the effects of a number of phenyl urethanes on animal tumours. Phenyl urethane and also isopropylphenylcarbamate (XVIII) were found to cause a significant inhibition in the growth of spontaneous mammary cancer in the mouse. The effect persisted only for so long as the drug was administered and soon disappeared when the latter was

withdrawn. Both these substances produced similar inhibition on the growth of the Walker rat carcinoma 256. Later it was found that ethyl carbamate (urethane) produces similar effects.

When urethane (XIX) and isopropyl phenylcarbamate were administered to cases of inoperable cancer in humans the effects on the tumours were slight but it was observed (by Paterson et al.[99]) that urethane in some cases caused a fall in the leucocyte count. This latter observation led to the administration of urethane to cases of leukaemia[99] and in a number of these favourable results were observed. Although in some cases the palliative effect was very great, it was not permanent and relapses may be observed and immature cells reappear in the blood. It is of interest that there is a close resemblance between the leucocyte responses to urethane and those brought about by X-ray treatment.

The examination of a number of miscellaneous substances for tumour inhibitory action has been made by various workers. For instance, Williams[79] tested suramin, several azo dyes and histamine without success: E. Boyland[87], in an extensive study on the chemotherapy of cancer, examined muscle extracts, heptaldehyde, citral, certain aromatic bases including benzidine, 4:4'-diaminodiphenyl ether and 4:4'-diaminodiphenyl sulphoxide. With some of these materials inhibitory effects of varying

degree were observed on animal tumours, the effect usually lasting only so long as the drug was administered. Apparently the results have not justified trials in human subjects.

Arising out of work on the physiological effects of mustard gas and some of its nitrogen analogues (the so-called "nitrogen mustards") in connection with chemical warfare research, it has been found that methyl-bis(β-chloroethyl)amine (HN2)(II) and tris-chloroethylamine(III) are of special interest[115a]. The use of tris-chloroethylamine has had to be abandoned because of its toxicity. Investigations on the effects of HN2 on cancer of the lung in humans have been made and varying degrees of amelioration, some very marked, were observed, but the effects were usually transient. Good but temporary responses to HN2 were also shown by Hodgkin's disease[115a]. It is not possible to assess the final usefulness, if any, of this compound at this stage. In a recent study, Rhoads[112] has emphasised that the nitrogen mustards are not a cure for those neoplastic diseases which have been studied. In large enough doses they are injurious to many kinds of tissues, exerting their maximum effect on rapidly growing tissue either normal or malignant.

Recently it was claimed[85] that pteroyl-γ-glutamyl-γ-glutamylglutamic acid ([redacted]) (see note IV) is identical with the active fermentation L. casei factor. This factor

has been shown to cause complete regression of about one third of spontaneous breast tumours in treated mice. The substance is now being tested on cases of inoperable human cancer but it is too early to assess its value in this field. However, preliminary results indicate that continued trials may be of interest. The fermentation factor was formerly thought to be folic acid but the latter compound has now been shown to be inactive.

A different approach to the problem of the growth inhibition of tumours was made some years ago by Haddow[1]. In the initial experiments the influence of polycyclic aromatic hydrocarbons on the growth of implanted tumours in rats was investigated and it was found that certain of these substances (e.g., 1:2:5:6-dibenzanthracene (V) or 3:4-benzpyrene (VI)) when injected into rats caused a significant inhibitory effect on the growth of the tumours. Those substances which produced inhibition also had the property of producing cancer on prolonged application in rats, whereas a number of non-carcinogenic, polycyclic aromatic hydrocarbons (e.g., phenanthrene and anthracene) were completely devoid of inhibitory effect. In a series of papers[1-7] published from 1937-1942 Haddow and his collaborators considerably expanded this earlier work and in general the initial results were confirmed. However, at the time of these early investigations the important effect of diet, particularly

the protein content of the diet, on the tumour inhibitory process had not been discovered. This aspect of the problem is discussed briefly below.

Elson, Haddow and their collaborators[80-84, 115b], in a study of the effect of the carcinogenic hydrocarbon 1:2:5:6-dibenzanthracene (hereafter referred to as DBA) on the growth of normal rats when the protein content of the diet was varied over a considerable range, found that the growth of the animals maintained on a high protein diet (20% protein) was, for an initial period, little affected by treatment with DBA. Later these animals lost weight rapidly and died. On the other hand, rats maintained on a low protein diet (10%) showed immediate growth inhibition on treatment with DBA, but these animals survived longer than those similarly treated on the high protein diet. The diets were made up so as to possess approximately the same calorific value. The authors concluded that, since the growth inhibitory action of the DBA is dependent on the protein content of the diet, then the growth inhibitory action of carcinogenic hydrocarbons of this type is brought about by direct interference with protein metabolism resulting in the prevention of protein synthesis.

If the tumour inhibitory properties of DBA are related to its inhibition of body growth, then it seemed probable that the protein content of the diet would also affect the former property.

This was a point of considerable interest in view of the earlier work of Haddow and his collaborators and was investigated by Elson and Haddow[82]. They found "that the mechanism of the tumour inhibitory action of DBA appears to be essentially the same as that of its body growth inhibition. Both are influenced to a large extent by the protein content of the diet and it is suggested that the inhibition is caused by interference with the availability, or with the actual synthesis of protein necessary for cellular growth." With animals on a low protein diet (5 or 10% protein) complete growth inhibition could be obtained for a long period. However, it was not possible to inhibit the growth of the Walker rat carcinoma 256 completely in these animals although a very considerable slowing down of the growth rate of the tumour is obtained. Finally, a stage is reached when the growth of the tumour at the expense of the normal body tissues becomes the predominant factor. The authors conclude that "it is highly probable that complete control of tumour growth is not attainable with an inhibitor of the type of DBA and could only be achieved by a substance having a more specific action on tumour cells. There is no evidence that DBA has such specific action."

The same authors found that the tumour inhibitory action of 2'-chloro-4-dimethylaminostilbene[84,115c] (VII) also depends on the protein content of the diet. On a 20% protein diet

almost no tumour inhibitory action on the Walker carcinoma 256 was shown, whereas on a 5% protein diet a very marked inhibition was obtained. In this case, however, growth inhibitory action seemed to be relatively greater on the tumour than on the body growth of the animal (the reverse was the case with DBA). This seems to indicate that the growth inhibitory action shown by this stilbene derivative may be associated with a more specific effect on the synthesis of protein required by the tumour cell. A number of other stilbene derivatives have been examined by Haddow and his collaborators[84,115c] for tumour inhibitory action and several of the amino compounds (e.g., 2'-methyl-4-dimethylaminostilbene (VIII) and α-(p-dimethylaminophenyl)-β-(α-naphthyl)-ethylene (IX)) were reported to have a very marked activity. In all these cases too, incorporation of a sufficiently high percentage of protein in the diet greatly diminished or completely abolished the inhibitory effect. It should be noted that all these aminostilbenes were subsequently shown to be carcinogenic. The problem of the connection of protein metabolism and the process of carcinogenesis brought to light by these initial experiments is being further studied. Although the growth inhibitory effects of the compounds first studied are not likely to be of any therapeutic value, the subsequent development of the investigation may lead to a greatly

increased knowledge of the mechanism of the process of carcinogenesis. At the present time this would seem to be one of the most important needs if a more hopeful approach to the problem of chemotherapy of cancer is to be made later.

The dependence of the carcinogenic activity of carcinogenic compounds on diet is not limited to the carcinogenic aromatic hydrocarbons and the aminostilbenes but is exhibited also by the carcinogenic azo dyes[101-110]. Indeed, a relation between the carcinogenicity of a carcinogenic compound and diet seems to have first been recognised in studies with the latter compounds. Japanese workers[101,102] found that liver tumours are readily produced in rats fed on a diet of carrots and polished rice to which p-dimethylaminoazobenzene (X) ("butter yellow") had been added in oil; but when 10-15% of liver or yeast[101] was added to the diet, or when the basal diet was wheat[102], the incidence of tumours was considerably reduced. American workers have considerably expanded these earlier observations. The addition of caesin or riboflavin[103], of protein and B vitamins[104, 106], and of dried egg albumin[106] all reduced the incidence of liver tumours in rats fed on a basal diet containing p-dimethylaminoazobenzene. The addition of a detergent to the basal diet or the replacement of the corn oil used by mineral oil[105] also reduced tumour incidence. In addition to these substances of

anti-carcinogenic effect others have been found which exert a co-carcinogenic action. Biotin apparently falls in this category[106]. The effect of a given dietary supplement has also been shown to depend on the particular carcinogenic azo dye used[107]. Although investigations[109,110] of these effects have been actively pursued their mechanism is not yet clear. However, it is probably different from that in the case of the carcinogenic aromatic hydrocarbons and their derivatives.

It may be noted that the aminostilbenes mentioned above are not oestrogenic. Growth inhibition caused by oestrogens probably differs from the retardation brought about by the non-oestrogenic carcinogenic compounds. For example, the action of oestrogens may be inactivated by a growth hormone as was shown by Griffiths and Young[86]. In addition Elson and Warren[81] have shown that stilboestrol inhibits the rate of tail growth of rats on a 20% protein diet, but that DBA has no effect under these conditions. Thus the inhibitory effect of stilboestrol is not related to the protein content of the diet as is that of DBA and the aminostilbenes. Also in contrast to stilboestrol, administration of pituitary growth hormone to rats maintained on a high protein diet and treated with DBA may bring about some increase in growth, but it appears at the same time to increase the toxic action of the DBA, since the growth increase is soon

followed by the death of the animals.

The discovery of Cook and Dodds[90] and of Cook, Dodds, Hewett and Lawson[91] that the potent carcinogenic hydrocarbons 5:6-cyclopenteno-1:2-benzanthracene (XI) and 3:4-benzpyrene possess a certain degree of oestrogenic activity, led to the examination of other carcinogenic hydrocarbons and certain of their derivatives for oestrogenic activity. As mentioned above, DBA was found devoid of activity but some of its 9:10-derivatives, notably 9:10-di-n-propyl-1:2:5:6-dibenz-9:10-dihydroanthraquinol (XII) showed considerable oestrogenic activity. Later this latter substance was found by Haddow and Robinson[2] to be strongly growth inhibitory and was also reported to be weakly carcinogenic[92].

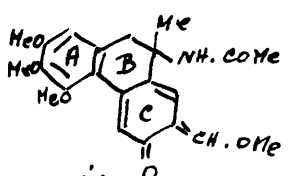
Continued investigation followed this earlier work on the relation of oestrogenic activity to molecular structure included the examination among other classes of compounds of various stilbene[93] and triphenylethylene derivatives[94]. Certain triphenylethylene and stilbene derivatives which had been shown to possess oestrogenic activity also showed tumour inhibitory action[7]. The treatment of patients with advanced cancer of the prostate with the strongly oestrogenic diethylstilboestrol (XIII) has been found in many cases to produce considerable clinical improvement. The usual results are relief of pain, partial regression of both the primary tumour and metastases and general

improvement in physical condition. Later tests were made with triphenylethylene derivatives. Favourable results were reported using triphenylchloroethylene[72a] (**XIV**). However, Haddow and Greene[72a] obtained relatively disappointing results in clinical trials using α-di-(p-ethoxyphenyl)-β-phenyl-β-bromoethylene (DBE) (**XV**). In this connection it may be noted that Buu-Hoï and his collaborators[88,89] in France have described the preparation of a number of triphenylethylene derivatives which have been examined for both oestrogenic and tumour inhibitory activity. One compound, viz. α-bromo-αββ-triphenylethylene (Y 59) (**XVI**) was found to be of some value in several cases of prostatic cancer. Partial or complete cessation of tumour growth was observed together with general physical improvement as long as administration of the drug was continued. The oestrogenic activity of Y 59 is less than that of stilboestrol and of DBE and the authors conclude that "the therapeutic efficacy of this type of substance against prostatic cancer does not depend on its oestrogenic activity and that the beneficial effects of oestrogens are not exclusively due to a 'biochemical castration'". There is no evidence available to show that cancer of the prostate can be cured by the use of oestrogenic substances, but the growth of both the primary tumour and the metastases may be arrested, accompanied in some cases by partial regression,

and relief of pain, improved physical condition and prolongation of life may be achieved.

It is evident from the results set out that progress towards a solution of the problem of a successful chemotherapy for cancer has been limited in spite of the considerable work in this field. Nor can this be regarded as surprising when the difficulty of the problem is considered. Haddow[72a] has recently emphasised that the cancer cell is but a modification of the normal somatic cell. Another serious difficulty is that the malignant variant of the normal cell is apparently quite permanent and only occasionally known to be reversible. Studies of the enzyme systems of normal and malignant tissues[96] have shown that tumours have qualitatively the same enzyme systems as normal tissues. The possibility of the discovery of enzymes unique to malignant tissues cannot, of course, be excluded in the present state of our knowledge, but as yet there is not evidence of the existence of such enzymes. With regard to the differences known to exist, one of the most notable is the relatively low content in tumours of aerobic catalytic systems, e.g., cyctochrome, cyctochrome c, succinic dehydrogenase, catalase, flavin, etc.[96,124]. These considerations make evident the difficulty of obtaining a chemotherapeutic agent specific only to the malignant cell and without action on normal and

particularly actively dividing tissues. Moreover, a chemotherapeutic agent for cancer would presumably have to bring about the destruction of every malignant cell in contrast to chemotherapeutic agents against microorganisms where a 100% extermination of the organisms by the agent is not essential for successful control of the infection. The body does not develop an immunity to cancer as it does after attacks of certain diseases. In spite of these serious difficulties the slight advances which have been achieved in recent times offer some encouragement for the continuance of the work.



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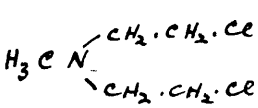

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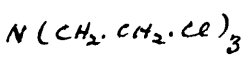

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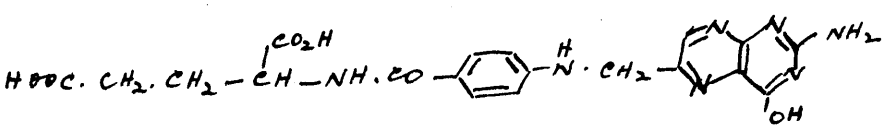
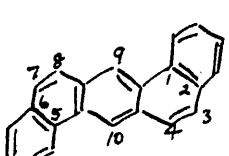
(IV) is believed to be a peptide of this acid



N- [4- {[(2-amino-4-hydroxy-6-pteridyl)methyl] -amino} -benzoyl] -ℓ (+)-glutamic acid.



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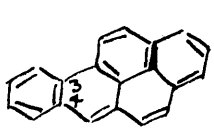

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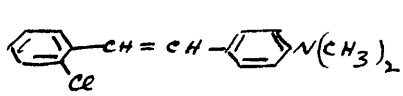

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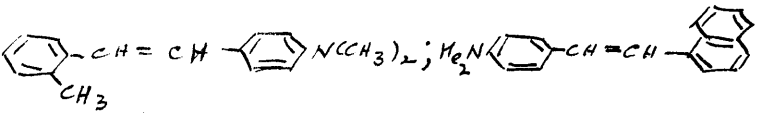

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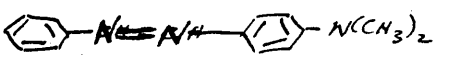

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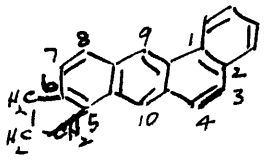

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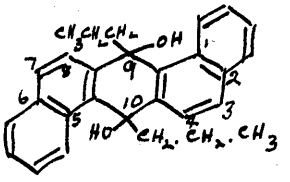

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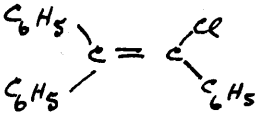

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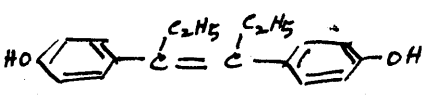

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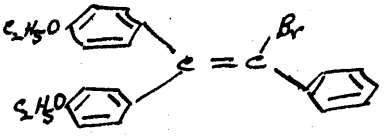

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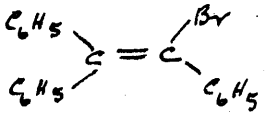

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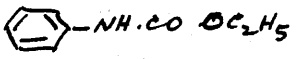

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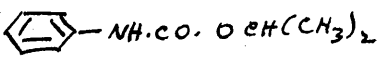

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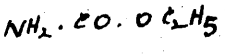

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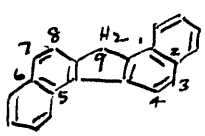
Part I.

Synthesis of (2':1'-Naphtha)-2:3-fluorene and of (1':2'-Naphtha)-1:2-fluorene.

Synthesis of (2':1'-Naphtha)-2:3-fluorene.

(a) Preliminary Investigations.

1:2:5:6-Dibenzfluorene (I) has feeble cancer producing activity[8]. It has also a very marked inhibitory effect on the growth of tumours[5]. Cook and Preston[9], as part of a search for compounds having a still more pronounced growth inhibitory activity, prepared a number of derivatives of 1:2:5:6-dibenzfluorene. Included in this programme was the synthesis of 2:3-(2':1'-naphtha)-fluorene (II).



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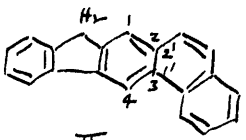

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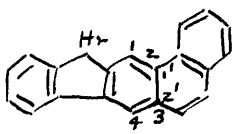
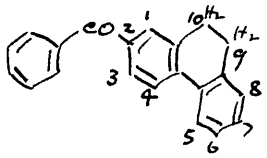


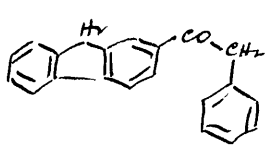
IIa



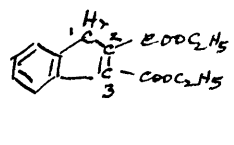
III

The following methods of synthesis were investigated by Cook and Preston. Since 9:10-dihydrophenanthrene normally undergoes substitution in position 2, it was expected that chloromethylation would take place in the same position. The resulting 2-chloromethyl compound could then be condensed with ethyl cyclohexanone-2-carboxylate, and procedures similar to those for the preparation of 2:3-(1':2'-naphtha)fluorene[10](IIa) should yield II. However, the product of chloromethylation of 9:10-dihydrophenanthrene was mainly the 3-substituted derivative. The Friedel-Crafts reaction between benzoyl chloride and 9:10-dihydrophenanthrene was then investigated and 2-benzoyl-9:10-dihydrophenanthrene (III) shown to be the main product. The corresponding carbinol was obtained by reduction of III with sodium amyloxide, but attempts to cyclise this to the

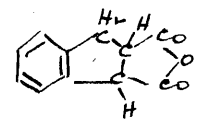
required fluorene failed. An Elbs pyrolysis on 2-phenylacetylfluorene (IV) was then tried but the results were not of practical value. It was hoped that the 2-β-phenylethylfluorene might undergo cyclodehydrogenation with aluminium chloride, but in view of the unsatisfactory results obtained from the Clemmensen reduction of 2-phenylacetylfluorene, this approach was abandoned. Finally, ethyl indene-2:3-dicarboxylate[11] (V) was



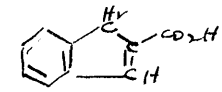
IV



V



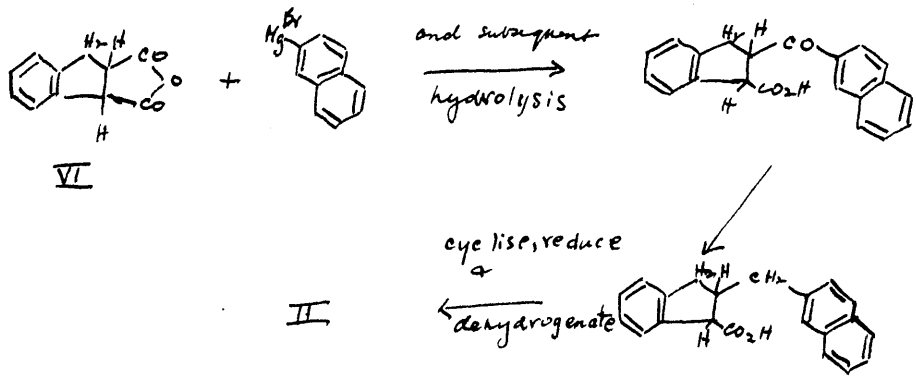
VI



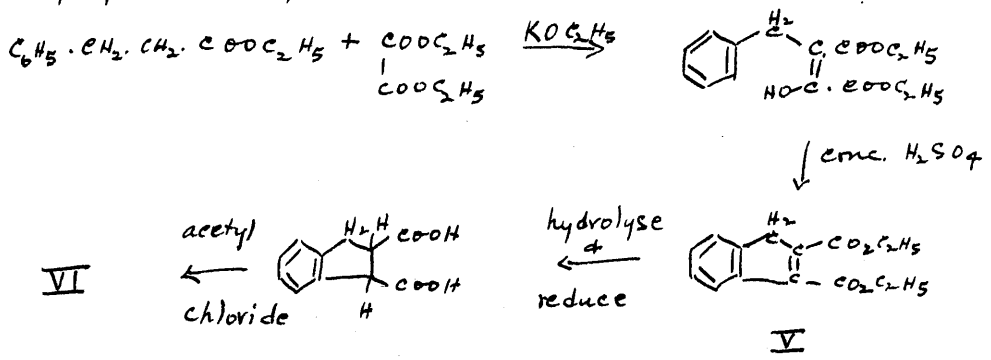
VII

converted into the anhydride (VI) of cis-indane-1:2-dicarboxylic acid, but the work was interrupted before the action of VI on β-naphthylmagnesium bromide could be examined (see below).

In the present investigation of the synthesis of 2:3-(2':1'-naphtha)-fluorene work was carried on from this point. It was proposed to condense the above anhydride with β-naphthylmagnesium bromide (cf. work of Weizmann and Bergmann, and of Fieser and others[12-17]) and complete the synthesis according to the scheme:



[For preparation of VI



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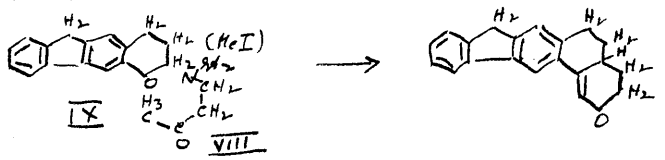
The condensation of VI with β-naphthylmagnesium bromide yielded, however, mainly neutral products which could not be identified and the scheme was abandoned. In the preparation of VI for the Grignard reaction several modifications of previous procedure were investigated. Cook and Preston (loc.cit.) had reduced ethyl indene-2:3-dicarboxylate catalytically and hydrolysed the indane diethyl ester so obtained with alcoholic potash to an acid of m.p. 228°, which they believed to be the cis-indane-1:2-dicarboxylic acid.. Professor Cook (unpublished data) subsequently showed it to be the trans acid and isolated the cis acid, m.p. 197°. Cook and Preston had converted the trans acid to the cis-indane-1:2-dicarboxylic acid anhydride using acetyl chloride, a process which was accompanied by a good deal of tar formation. The catalytic reduction of indene-2:3-dicarboxylic acid has now been investigated and shown to yield mainly the cis acid together with some unidentified oily

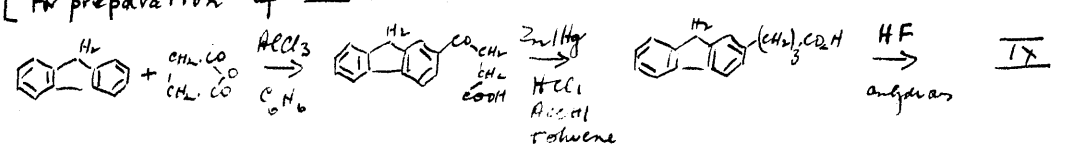
material. Ethyl indene-2:3-dicarboxylate was also reduced and submitted to acid hydrolysis, when a product consisting predominantly of cis acid was obtained. The cis acid is converted smoothly to the anhydride on treatment with acetyl chloride. A small quantity of the acid was also successfully converted to the anhydride by heating with tetrachloroethane (Mason's method[22]).

In connection with the above scheme, the action of VI on tetralin in nitrobenzene solution containing aluminium chloride was also examined, but again the product consisted mainly of neutral material which could not be identified.

The next approach to the synthesis of II was the investigation of the action of the methiodide of 1-diethylaminobutan-3-one (VIII) on ketotetrahydro-2:3-benzofluorene (IX). If the condensation took place as indicated, then subsequent reduction and dehydrogenation of the pentacyclic ketone should yield the required hydrocarbon. This method of adding a 6-ring to a suitable ketone was first employed by du Feu, McQuillan and Robinson[25], and subsequently extended by Wilds and Shunk[26], and by Cornforth and Robinson[27].



[For preparation of IX:



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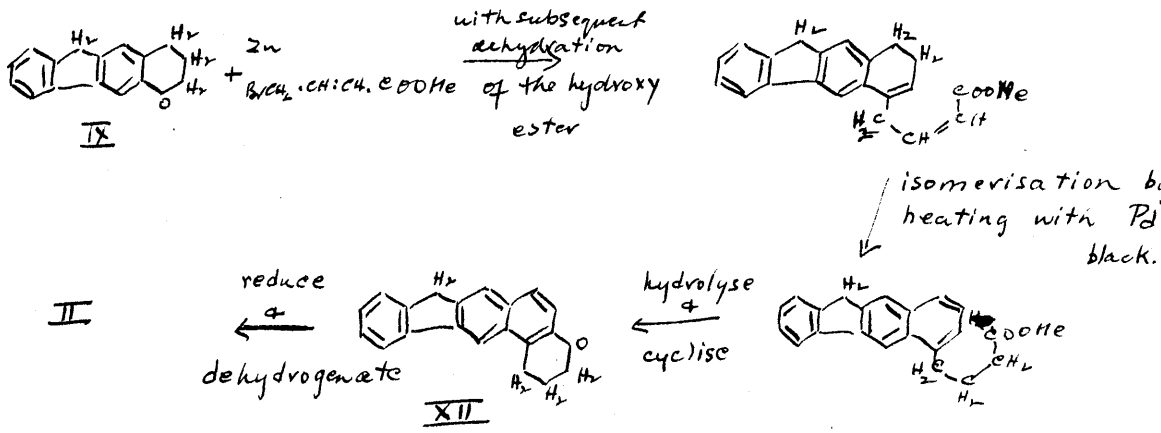
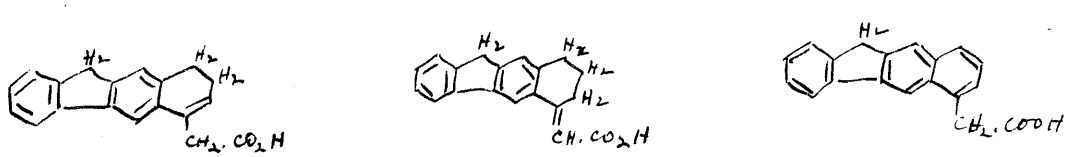
In a number of experiments using varying conditions, however, the ketone (IX) was recovered unchanged. Attempts were then made to build the desired 6-ring on to IX using a Reformatsky reaction involving γ-bromocrotonic methyl ester with subsequent isomerisation and cyclisation as described by Cook and Schoental[31] for 3-chrysenol. The scheme was as follows:-



The Reformatsky reaction (after hydrolysis) yielded reasonable amounts of an acidic product, but it was not found possible to purify it or the product of isomerisation obtained by treatment of the methyl ester of the crude acid with palladium black as described by Cook and Schoental (loc.cit.). In conjunction with this work the Reformatsky reaction on ketotetrahydro-2:3-benzofluorene and ethyl bromoacetate was examined. From this an acid corresponding to X or XI was isolated.



X XI XIII

Conversion of this acid to the dehydrogenated form XIII, lengthening the side chain of XIII by one of several standard procedures and subsequent cyclisation should lead to the desired pentacyclic ketone (XII). However, in view of the large number of steps involved, this approach to the synthesis of II was set aside in favour of the synthesis starting with 1:2:7:8-dibenzanthracene and described in a subsequent section (p. 37).

Experimental.

(In this and subsequent experimental sections all melting points are uncorrected).

β-Phenylpropionic acid was prepared by reduction of cinnamic acid with Raney's nickel aluminium alloy and aqueous sodium hydroxide essentially according to the method of Papa, Schwenk and Whitman[18,19]. Cinnamic acid (29.8 g.; 0.2 mol.) dissolved in 10% sodium hydroxide (900 ml.) was heated to 90° and maintained at 90-95° during the addition of the alloy (90 g.). The time of addition was 60-70 minutes and the mixture was heated a further 1-1.5 hours at 90-95°, allowed to cool, diluted with water and filtered, and the alloy washed well with water. The combined alkaline liquors were run in a thin stream, with constant stirring, into 750 ml. of concentrated hydrochloric acid. The hydrocinnamic acid which separated as an oil soon

solidified. It was collected, washed and dried on a porous tile. Yield 80-85% of the theoretical amount. M.p. 43-45°.

Ethyl β-phenylpropionate. β-Phenylpropionic acid (116 g.), absolute alcohol (350 ml.), and concentrated sulphuric acid (7 ml.) were mixed and refluxed for 3.5 hours. After distilling off 215 ml. of alcohol, the residue was diluted with ice water (500 ml.), the oily layer separated and the aqueous layer extracted 3 times with benzene. The combined ester and washings were washed with sodium carbonate solution and with water, dried over sodium sulphate, the benzene removed and the residue distilled under reduced pressure. Yield 106 g.; b.p. 124-6°/15 mm. A second fraction (12 g.) of b.p. 127-130°/18 mm. was obtained.

Ethylbenzyloxaloacetate (cf. method of K. v. Auwers[20]). 300 g. of absolute ether and 20 g. (0.513 g. atom.) of potassium pellets were placed in a 1 l. 3-necked flask fitted with a mercury-sealed mechanical stirrer, a dropping funnel, and a condenser, and the apparatus was protected from moisture with calcium chloride tubes. Stirring was commenced and absolute alcohol (30 g.) added dropwise over a period of ½-¾ hour. Stirring was continued for a further 1½ hours, when the bulk of the potassium had dissolved. Freshly distilled ethyl oxalate

(73 g.; 67.7 ml.; 0.5 mol.) was then added (15 minutes), the mixture being cooled occasionally with ice water. Stirring was continued for another ½-1 hour and ethyl-β-phenylpropionate (89 g.; 87.7 ml.; 0.5 mol.) was then added (15-20 min.). The solution had now acquired a deep orange or red colour. It was stirred for another hour, let stand overnight, heated with stirring for 3 hours, cooled, and decomposed with 500 ml. of ice water. The almost colourless ether layer was separated and the yellow aqueous layer extracted twice with ether. The combined ether extracts were washed with water, dried with sodium sulphate, the ether removed and the residual oil distilled under reduced pressure, when unchanged ethyl oxalate was first collected, and then unchanged ethyl-β-phenylpropionate; a small amount of a high boiling residue was discarded.

The aqueous layer (see above) was acidified with concentrated hydrochloric acid, when a pale yellow oil separated; the mixture was extracted 4 times with ether; the combined ether extracts washed with water, dried over sodium sulphate, and the ether removed. Yield of the residual oil 80-115 g. It was submitted to cyclisation without further purification. Wislicenus and Münzesheimer[21] state that ethylbenzyloxaloacetate cannot be distilled without decomposition even in vacuo.

Ethyl indene-2:3-dicarboxylate and indene-2:3-dicarboxylic acid.

The procedure of Bougault (loc.cit.) using concentrated sulphuric acid was modified as follows: ethylbenzyloxaloacetate (114 g.) was added with constant shaking to concentrated sulphuric acid (500 ml.; d 1.84). The addition occupied 3 minutes. The mixture became hot and developed a deep red colour. After standing 6-8 days at room temperature, the clear red solution was decomposed with crushed ice (1500 g.), when a pale yellow oil and traces of darker gummy material separated. The oily layer was extracted with benzene, and the benzene extract washed 3 times with sodium carbonate solution, the first alkaline extract being deep red and the others nearly colourless. The sodium carbonate washings on acidification yielded a light brown oil which on standing solidified to a sticky solid. Without further purification this was dissolved in acetic acid and concentrated hydrochloric acid (3 vols. acetic acid, 1 vol. of concentrated hydrochloric acid) and heated on the water bath until no further solid separated (3-5 hours). The solid was identified as indene-2:3-dicarboxylic acid. The original material was presumably one or both of the half esters. The benzene extract (see above) was washed with water, dried over sodium sulphate, and the benzene removed under reduced pressure, when a pale yellow oil remained, which solidified to a pale

yellow crystalline solid on cooling. Draining on a porous tile gave colourless crystals of m.p. 73-75°, which crystallised from petroleum ether (40-60°) had m.p. 76-78°. The bulk of the ester was dissolved in acetic acid/concentrated hydrochloric acid (3:1) and heated on the water bath until the separation of the solid, which began after 2-3 hours, was complete (4-6 hours). The mixture was diluted with ice water and the indene-2:3-dicarboxylic acid collected and washed. It was a cream coloured powder, m.p. 220-222° (decomp.; the m.p. may be varied appreciably depending on the rate of heating). This product was quite satisfactory for hydrogenation without further purification. Purification of large quantities of this acid was not attempted owing to its sparing solubility in the usual organic solvents and the ease with which it is decarboxylated to indene-2-carboxylic acid (VII). For instance, decarboxylation is effected by boiling for a short time in dilute acetic acid or in water, the latter procedure gives a cleaner product.

Reduction of indene-2:3-dicarboxylic acid. The acid (5.1 g.; 0.025 mol.) was suspended in alcohol (400 ml.), and shaken with 2 g. of a palladium/charcoal catalyst[23] or with 0.1 g. of a palladium black catalyst[24] and hydrogen (at approximately atmospheric pressure) until absorption ceased (about 10% in excess

of the theoretical volume was usually absorbed). After removal of the catalyst the alcohol was evaporated under reduced pressure leaving a sticky solid, from which the oily material was removed by rubbing with a little ethyl acetate. The acid crystallised from water had m.p. 190-192° (decomp.; the m.p. can be varied appreciably depending on the rate of heating). Yield 2.5 g. The residual oil left after removal of the ethyl acetate was dissolved in acetic acid/concentrated hydrochloric acid (3:1) and heated until no more solid separated (ca. 4 hours). The solvents were evaporated, and the pale brown crystalline sticky residue worked up as the first fraction, when additional 1.2 g. of acid m.p. 186-188° (decomp.) was obtained. Apparently some esterification occurred during reduction.

Acid hydrolysis of ethylindane-1:2-decarboxylate. Ethyl indene-2:3-decarboxylate (2.6 g.) was reduced as described by Cook and Preston (loc.cit.). No attempt was made to induce the oily product to crystallise, but it was dissolved in acetic acid/concentrated hydrochloric acid (3:1) and refluxed until a drop of the solution gave no turbidity on dilution with water (ca. 4 hours). Considerable crystalline material was now present and more separated on dilution with water. The colourless crystalline product was collected and washed with a little water. Yield 1.86-1.91 g. M.p. 187-189° (decomp.).

cis-Indane-1:2-dicarboxylic acid anhydride.

(a). cis-Indane-1:2-dicarboxylic acid (2.4 g.) and freshly distilled acetyl chloride (10 ml.) were refluxed, when the solid dissolved after 1 hour's heating to give a clear, pale brown solution. After 4-5 hours the bulk of the acetyl chloride was distilled off, and the rest removed in vacuo over sodium hydroxide. The crystalline residue was rubbed with a little dry ether to remove oily matter, filtered and washed with ether. Yield 1.4 g. of colourless crystals. M.p. 97-98°.

(b). 0.14 g. of cis-indane-1:2-dicarboxylic acid was mixed with 10 ml. of dry tetrachloroethane, and the mixture heated in an oil bath so that the solvent slowly distilled. The last traces were removed by heating at 150°/23 mm. A pale brown oil remained which on standing deposited crystals. Rubbing with a 1:1 mixture of dry benzene/cyclohexane gave colourless crystals of m.p.96-98°.

Action of β-naphthylmagnesium bromide on cis-indane-1:2-dicarboxylic acid anhydride. β-Naphthylmagnesium bromide (prepared from 17 g. of β-bromonaphthalene, 2 g. of magnesium and 60 ml. of absolute ether) was added to a warm mixture of 15.4 g. (0.082 mol.) of indane dicarboxylic acid anhydride (5-10 minutes) in absolute ether (60 ml.) and benzene (sodium dried, thiophene free, 70 ml.), when there was an immediate separation of a bulky yellow precipitate and the mixture boiled briskly. After refluxing for 2 hours and standing at room temperature

for 36 hours the reaction mixture was decomposed with ice and dilute sulphuric acid. The ether/benzene layer was separated, washed repeatedly with sodium carbonate solution and then with water, the solvents removed, and from the semi-solid residue naphthalene was isolated by sublimation, and converted to its picrate of correct m.p. and no depression with an authentic specimen. A small amount of a material of m.p. 182.5-184° (giving a picrate of m.p. 182.5-184° (depression of m.p. when mixed with the original substance)) was also isolated and was presumably 2:2'-dinaphthyl.

From the sulphuric acid layer a considerable amount of brown gummy material separated. It was collected, washed and extracted with sodium carbonate solution and the extracts combined with those of the benzene layer (see above). The material which separated on acidification was shown to consist mainly of cis-indane-1:2-dicarboxylic acid and no other solid could be isolated from this acid fraction. There was a considerable amount of oily material insoluble in sodium carbonate solution. It was not found possible to obtain any appreciable quantity of crystalline material from this and vacuum distillation failed to give any useful results.

The action of cis-indane-1:2-dicarboxylic acid anhydride on tetralin dissolved in a solution of aluminium chloride in

nitrobenzene was then investigated. Tetralin was selected instead of naphthalene since substitution would be expected to take place exclusively in the β-position. Indane-1:2-dicarboxylic acid anhydride (1.3 g.), and tetralin (1.1 g.) were mixed and added to 2.2 g. of aluminium chloride dissolved in 15 ml. of dry, pure nitrobenzene and cooled to 0°. The mixture became orange brown. It was retained in the ice bath for 12 hours and then at room temperature for 4 days. The reaction mixture was decomposed with ice and dilute hydrochloric acid in the usual way and steam distilled to remove the nitrobenzene, when a brown, hard, resinous material remained. On extraction with aqueous sodium carbonate a trace of cis-indane-1:2-dicarboxylic acid was recovered, but the bulk of the product was neutral. It could not be caused to crystallise and was vacuum distilled, but the various fractions of the distillate were oils which could not be induced to crystallise.

Ketotetrahydro-2:3-benzofluorene (IX) was first prepared by Koelsch[28] and the procedure slightly modified by Lothrop and Coffman[29]. Under Friedel-Crafts conditions succinic anhydride reacts with fluorene mainly in the 2-position and the resulting 2-fluoroyl propionic acid is reduced by Clemmensen reduction to γ-2-fluoryl-butyric acid, which is cyclised by anhydrous hydrogen fluoride to the required ketone in excellent yield.

β -Fluoroylpropionic acid was prepared using exactly the quantities and conditions given by Koelsch (loc.cit.), but it was found more convenient to purify the crude product by crystallisation from dioxane, when it was obtained as colourless needles, m.p. 211-212°. Yield 70-80% of the theoretical amount.

γ-Fluorylbutyric acid. When the reduction was carried out according to the directions of Koelsch the product was difficult to purify. The Martin modification[30] of the Clemmensen reduction method gave good yields of a purer product. Granulated zinc (140 g.) was amalgamated according to Martin's method[30a] after preliminary cleaning with dilute hydrochloric acid. To it were added in the order named, acetic acid (480 ml.), toluene (280 ml.), concentrated hydrochloric acid (300 ml.) and β-fluoroylpropionic acid (60 g.), and the mixture was refluxed for 50 hours, 60 ml. of concentrated hydrochloric acid being added every 10 hours until a total of 540 ml. had been added to the mixture. After decanting from the residual zinc the mixture was steam distilled to remove the toluene, and diluted with 200 ml. of concentrated hydrochloric acid. The crude γ-fluorylbutyric acid was collected, washed with dilute acid and then with water and crystallised from 80% acetic acid, filtering hot to remove a small amount of a high melting impurity. Yield 48-53 g. of colourless solid of m.p. 150-151°.

Ketotetrahydro-2:3-benzofluorene. Finely powdered γ-fluoryl-butyric acid was added to a large excess of anhydrous hydrogen fluoride in a platinum dish at room temperature (ca. 10°), the mixture was stirred well, covered, and allowed to stand overnight. The residual hydrogen fluoride was allowed to evaporate and the alkali insoluble material crystallised from alcohol or sublimed in vacuo. Colourless crystals, m.p. 149-150°. Yields better than 90% (cf. Lothrop and Coffman[29]).

1-Diethylaminobutan-3-one was prepared essentially according to the directions of Wilds and Shunk (loc.cit.) but 3 times their quantities were used. It was necessary to distil the product 3 times in vacuo to free it from high boiling impurities. It was obtained as a colourless oil b.p. 67-69°/11 mm. The methiodide was prepared according to the directions of Wilds and Shunk.

The attempted condensation of the methiodide of VIII with IX was carried out in the presence of alcoholic sodium ethoxide and of sodium methoxide in methanol/benzene solution. From all experiments a large proportion of the ketone was recovered unchanged, and if heating of the reaction mixture had been prolonged, small quantities of a high melting substance (that was not identified). It was also shown that prolonged refluxing of ketotetrahydro-2:3-benzofluorene with alcoholic sodium ethoxide

gives rise gradually to the same high melting product.

N-bromosuccinimide was prepared according to the method of Ziegler et al.[32] The methyl crotonate was prepared according to the method of Purdie and Marshall[33]. The γ-bromocrotonic methyl ester was prepared according to the method of Ziegler (loc.cit.), carbon tetrachloride being used as solvent.

The Reformatsky reaction between IX and γ-bromocrotonic methyl ester was tried under varying conditions, of which the following seemed most satisfactory. Arsenic-free zinc (activated according to the method of Fieser and Johnson[34]) (2.6 g.) was placed in a 250 ml. 3-necked flask fitted with a mercury sealed mechanical stirrer, a dropping funnel and a condenser, and the apparatus was protected from moisture with calcium chloride tubes. The zinc was heated with a little benzene and mercuric chloride, the ketone (4.7 g.; 0.02 mol.), dissolved in benzene was added with stirring, and then the γ-bromocrotonic methyl ester (5 ml.) in benzene (a total of 120 ml. of sodium dried, thiophene free benzene was used for the experiment) was run into the still warm mixture. If the reaction did not commence after a few minutes, the mixture was refluxed on the water bath, when the separation of the addition complex soon commenced. The mixture was heated and stirred for 3 hours. Substitution of a mixture of benzene and toluene for benzene, or a shorter time

of refluxing gave even less satisfactory results. Methanol was then stirred into the still warm mixture[34], when most of the addition complex dissolved. The solution was decanted from the residual zinc which was washed with methanol/benzene. The yellow benzene/methanol solution was shaken with dilute hydrochloric acid, washed with water (twice), and the benzene removed under reduced pressure. The yellow semi-solid residue contained considerable quantities of unchanged ketone which could be recovered by vacuum distillation, but attempts to vacuum distil the higher boiling fractions remaining after removal of the ketone lead to widespread decomposition (pressure ca. 0.2 mm.). The crude mixture was therefore subjected to hydrolysis by alcoholic sodium hydroxide, when a deep brown colour developed, which was not prevented by carrying out the hydrolysis in an atmosphere of nitrogen. The product was poured into water and extracted several times with chloroform to remove ketone and some of the dark colouring matter. On acidification of the filtered aqueous layer a brown powdery solid was obtained (yield 40-60% of the theoretical amount without allowing for unchanged ketone). Acid hydrolysis of the crude mixture did not prove satisfactory. Dehydration of the crude hydroxy ester with thionyl chloride[37] or phosphorus pentoxide[36] before hydrolysis did not improve the product. It was not found possible to purify the crude acid

and it was esterified either with ethereal diazomethane or by refluxing (12 hours) with methanol saturated with anhydrous hydrogen chloride. By either method a light reddish brown solid was obtained which appeared to be crystalline when examined under the microscope. It was not found possible, however, to purify it by crystallisation and vacuum distillation was not satisfactory. The crude ester was subjected to isomerisation by heating with palladium black[24] (1/10 or more of the weight of the ester was used) in a nitrogen atmosphere at various temperatures[31], but before sufficient temperature to allow isomerisation could be obtained, much darkening of the material always took place. The various methods (crystallisation, distillation in vacuo, chromatography on silica) tried for the purification of the product were unsuccessful; and this was also the case with the acid obtained on its hydrolysis. Finally, the crude acid was treated with anhydrous hydrogen fluoride, when a large proportion of an alkali insoluble brown powder was formed which could not be crystallised. Subjected to chromatography (on alumina) a large number of bands were obtained. After elution of these a positive test with phenylhydrazine was obtained with one of them, but the quantity of crystalline material was insufficient for further purification. The action of anhydrous hydrogen fluoride on the unisomerised acid was examined, but no satisfactory result could be obtained.

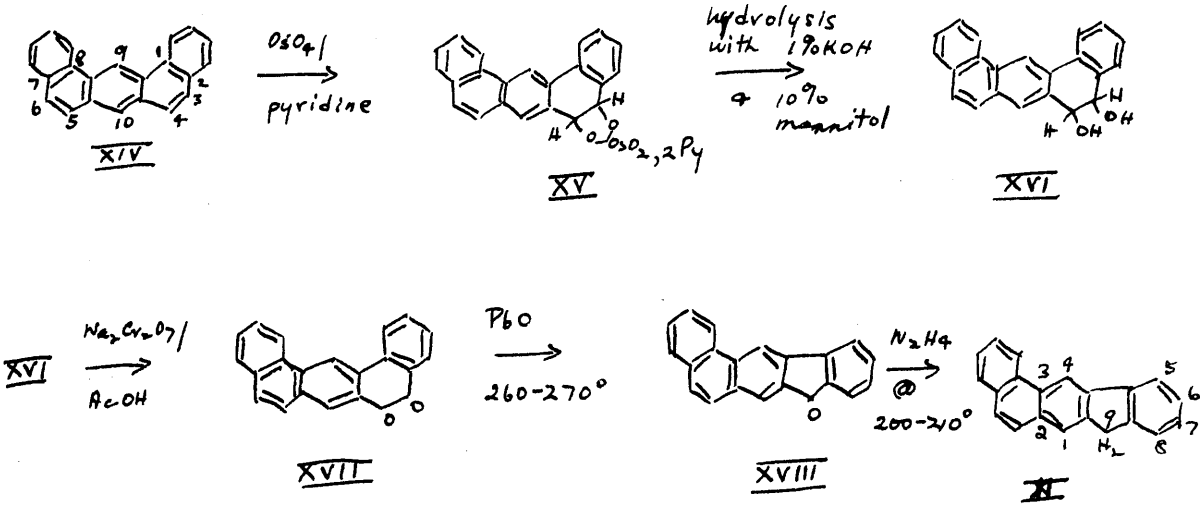
Reformatsky reaction on ketotetrahydro-2:3-benzofluorene and ethyl bromoacetate. The apparatus and procedure used for the case of γ-bromocrotonic methyl ester were satisfactory. It was found best to dehydrate the resulting ester (by refluxing a benzene solution of it with phosphorus pentoxide) before hydrolysis with alcoholic potassium hydrogide in a nitrogen atmosphere. The hydrolysis product was poured into water, extracted repeatedly with chloroform, and the filtered aqueous layer on acidification gave 3 g. of crude acid form 4.7 g. of ketone used initially (in none of these experiments was it practicable to recover the unchanged ketone, as it was obtained again in a very impure state difficult to purify). The crude acid was purified through its potassium salt, the latter being fractionally precipitated from an alcoholic solution by ether, decanting from the tarry matter which first separated. The product was a light brown powdery material readily soluble in water, from which the acid was precipitated on acidification. Crystallised from benzene, it had m.p. 166-167.5°. Yield 1.4 g. (25% of the theoretical amount if no allowance for unchanged ketone is made). A portion for analysis was crystallised from petroleum ether in which it is sparingly soluble. Colourless needles, m.p. 167-168° (decomp.).

(Found: C, 82.9; H, 5.6. $C_{19}H_{16}O_2$ requires C, 82.6; H, 5.8%).

Synthesis of (2':1'-Naphtha)-2:3-fluorene.

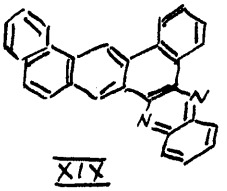
(b) Introduction to Experimental.

(2':1'-Naphtha)-2:3-fluorene (II) was eventually synthesised according to the following scheme:

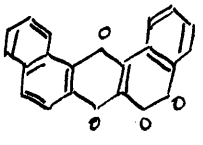


Criegee, Marchand and Wannowius[64] found that phenanthrene reacts with osmium tetroxide and pyridine to give an osmium containing complex, which on hydrolysis with dilute alkali gave 9:10-dihydroxy-9:10-dihydrophenanthrene in good yield. This reaction was recently extended by Cook and Schoental[65] to a number of other polycyclic, condensed ring aromatic hydrocarbons. The point of attack in the molecule was often not that place which is most usually attacked by chemical reagents. For example, 1:2-benzanthracene gave exclusively the 3:4-diol. This diol was identified by conversion to the corresponding phenol by dehydration, the methyl ether of the latter being identical with synthetic 3-methoxy-1:2-benzanthracene[70].

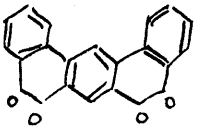
Moreover this diol was oxidised by chromic acid to the known 1:2-benz-3:4-anthraquinone[71]. It seemed highly probable from this result that in the case of 1:2:7:8-dibenzanthracene (XIV) osmium tetroxide would react in the 3:4-position to give the diol (XVI). It was found that the mono-quinone formed by cautious oxidation of the diol from 1:2:7:8-dibenzanthracene was an ortho quinone (it condensed readily with o-phenylene diamine forming a quinoxaline derivative (XIX)) and not the known 1:2:7:8-dibenz-9:10-anthraquinone[66]. Oxidation of XVI was carried out with sodium dichromate in acetic acid, but in spite of a considerable variation in conditions the required quinone (XVII) was always contaminated with appreciable amounts of a very sparingly soluble orange byproduct, which analyses as a di-quinone and presumably has the structure XXI and not XX since with o-phenylene diamine it forms a di-phenazine derivative (XXIa). It was not found possible to effect a complete separation of the mono-quinone (XVII) from the oxidation product by crystallisation, but it was finally obtained pure by cautious vacuum sublimation. Further attack on the diol (XVI)



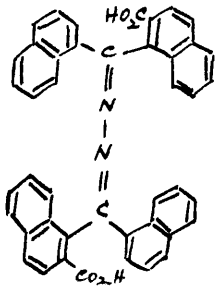
XIX



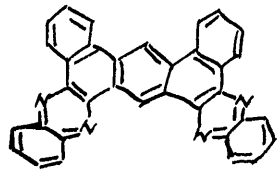
XX



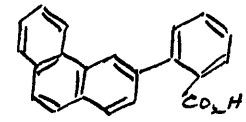
XXI



XXVI



XXIa



XVIIa

by the dichromate, a strong oxidising agent, might be expected and other methods of oxidation were examined. Heating with copper sulphate and pyridine caused either no effect or, on prolonged heating, some fission of the bond apparently took place with production of acidic materials. On boiling with chloranil in xylene the diol was gradually converted to a dark mass from which no quinone was isolated. The diol was probably dehydrated to the 3 or 4-phenol which is readily oxidised to black materials (see below). Following a report by Boyland 100 of the preparation of phenanthrene quinone from 9:10-dihydroxy-9:10-dihydrophenanthrene by oxidation with permanganate, this procedure was applied to XVI but only traces of quinone were obtained. It has recently been found (Miss J.Campbell) that when a mixture of pyrene diol, methylene chloride and dilute aqueous potassium hydroxide is shaken for some hours in the presence of air, the diol is oxidised to the corresponding quinone in good yield. In the present case, however, this oxidation was too slow to be of value. When XVI was heated with azodicarboxylic acid diethyl ester cf. 131 at 100-110° for some

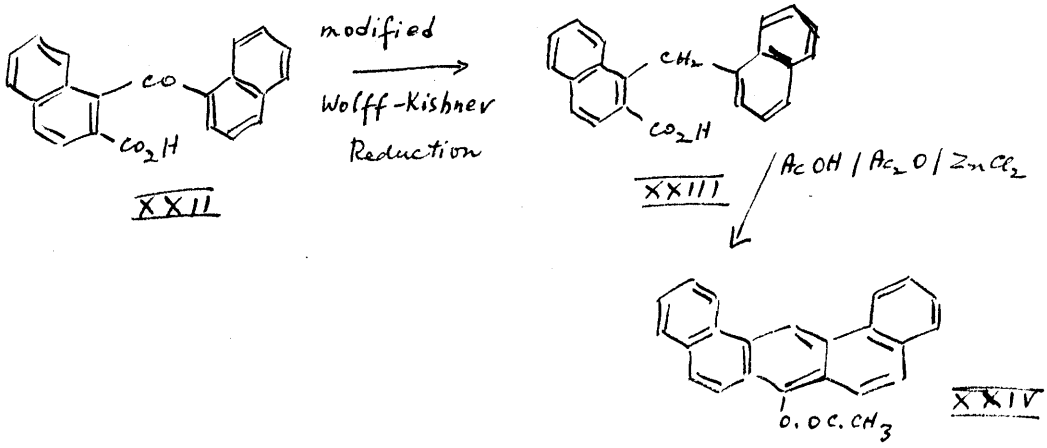
hours oxidation to the quinone XVII took place in moderate yield and no contamination with the orange impurity was detected. No products of Diels-Alder reaction between XVI or XVII were detected but since the arrangement of bonds typical of anthracene no longer exists in XVI and XVII, this is not to be expected.

Conversion of XVII to the required (2':1'-naphtha)-2:3-fluorenone (XVIII) took place smoothly on heating with litharge and the product was sublimed from the reaction mixture, when it was placed under reduced pressure. The mechanism of the reaction using litharge under these relatively drastic conditions is not certain, but if the acid XVIIa were an intermediate in the reaction it might possibly cyclise to give (1':2'-naphtha)-1:2-fluorenone (XXXII) and not the required (2';1'-naphtha)-2:3-fluorenone. In confirmation of the structure XVIII the analogous transformation with 1:2-benzanthracene-3:4-quinone was studied. The two ketones theoretically possible in this case are 1:2-benzfluorenone and 2:3-benzfluorenone, both of which are known. When pure 1:2-benzanthracene-3:4-quinone was treated with litharge under exactly the same conditions as those used with 1:2:7:8-dibenzanthracene-3:4-quinone a ketone of m.p. 149-151° (150.5-152.5° after crystallisation from alcohol) was obtained agreeing in properties with the known

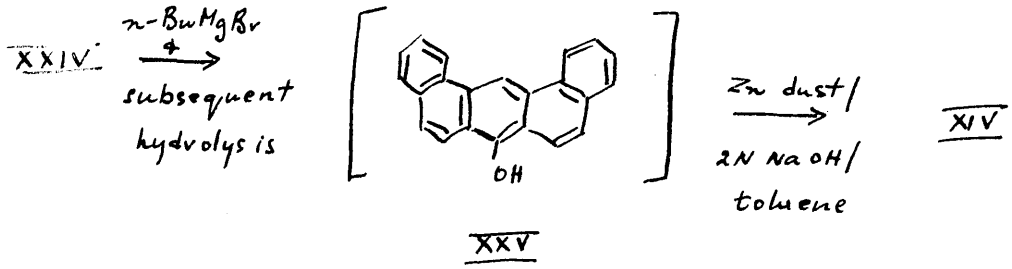
2:3-benzfluorenone. It was converted to its oxime m.p. 230-231° (decomp.) (2:3-benzfluorenone oxime has m.p. 231°. 1:2-Benzfluorenone has m.p. 132.5°, oxime m.p. 202° (decomp.)). No 1:2-benzfluorenone was detected in the sublimate from the litharge fusion. It is highly probable that the reaction with the 1:2:7:8-dibenzanthracene-3:4-quinone proceeds in an analogous manner and that the ketone thus obtained is therefore (2':1'-naphtha)-2:3-fluorenone (XVIII).

(2':1'-Naphtha)-2:3-fluorenone was reduced to (2':1-naphtha)-2:3-fluorene (II) by heating with hydrazine hydrate in a sealed tube. Attempts to apply Huang Minlon's modification[67] of the Wolff-Kishner method to this reduction were not successful although the modification gave satisfactory yields of fluorene from fluorenone.

The 1:2:7:8-dibenzanthracene needed for the above synthesis is not available commercially and it was found desirable to modify the synthesis of Cook[66] in several particulars. The scheme of synthesis is set out below:



XXII XXIII XXIV



2-Carboxy-1:1'-dinaphthyl ketone (XXII) was prepared according to the method of Cook[66]. Cook reduced this keto acid with zinc dust and dilute potassium hydroxide, but the resulting 2-carboxy-1:1'-dinaphthylmethane (XXIII) could not be purified and was used in the crude state for cyclisation. A crystalline product has now been obtained from the crude reduction product after submitting it to chromatography on silica, but the yield was poor. Considerably better yields were obtained by applying Huang-Minlon's modified[67] Wolff-Kishner method to the reduction of XXII, and XXIII has now been obtained analytically pure. A very sparingly soluble by-product, corresponding in analysis to the azine XXVI (see formula p.39), was always formed in these reductions in spite of considerable variations in the proportion of the hydrazine used. This modification of the Wolff-Kishner reduction is a useful alternative method to the zinc dust/alkali reduction of this type of keto acid, and is superior to catalytic hydrogenation in so far as the naphthalene nuclei are not subject to the risk of reduction.

2-Carboxy-1:1'-dinaphthylmethane was cyclised smoothly to 1:2:7:8-dibenzanthranyl-10-acetate (XXIV) in good yield. XXIV could not be reduced directly with zinc dust and dilute alkali because of the difficulty of hydrolysing the acetate under these conditions. Use of concentrated alkali (which effected hydrolysis of the acetate) and zinc dust was undesirable because of the possibility of reducing the naphthalene residues. However, following the procedure of Fieser and Hershberg[68], the acetate was readily split by refluxing with excess of n-butyl magnesium bromide. The anthranol (XXV) was not isolated but reduced immediately according to Martin's procedure[69] to give 1:2:7:8-dibenzanthracene (XIV) in fair yield.

Experimental.

2-Carboxy:1:1'-dinaphthylketone (XXII). In the oxidation of 2-methyl-1:1'-dinaphthylketone it was found that freshly prepared and sublimed selenium dioxide gave no better yields than samples of commercial selenious acid (B.D.H.). Because of the shortage of suitable glass tubing attempts were made to carry out the reaction on the same scale in a small stainless steel autoclave, but the product was either a dark gum or a sample of XXII of inferior quality. In working up the product (from the sealed tubes) it was found more convenient to dissolve the crude

ketone/keto acid mixture (after washing free from selenious acid) in chloroform, and to extract the keto acid with sodium carbonate solution. The acid recovered by acidification of this extract had m.p. 232-234°, and after crystallisation from acetic acid (charcoal) it had m.p. 239-240°, and was suitable for reduction. The crude ketone remaining after removal of the chloroform was used for further oxidations without preliminary purification.

2-Carboxy-1:1'-dinaphthylmethane (XXIII). (a). In view of the persistent formation of the azine (XXVI) as byproduct, the proportion of hydrazine used in the modified Wolff-Kishner reduction was varied considerably. When equimolar proportions of hydrazine and the keto acid were used, a yield of about 25% of XXIII and a large proportion of XXVI were obtained. Increase of the proportion of hydrazine to 4 moles increased the yield of XXIII to approximately 50%, but considerable azine was still formed. Further increase of hydrazine to 8 moles did not improve the yield of XXIII, but its quality decreased with this large excess of hydrazine. The proportion of azine formed also increased. The reason for this behaviour is not clear. The following procedure was found satisfactory and details of a typical experiment are: the keto acid (X XII) (3.26 g.; 0.01 mol.), 90% hydrazine hydrate solution (2.21 ml.), potassium

hydroxide (1.9 g.), and diethylene glycol (25 ml.) were mixed and boiled gently under reflux for 1.5 hours. The water condenser was then removed and the temperature of the mixture (thermometer in liquid) allowed to rise to 190-195°. The condenser was replaced and the mixture refluxed for a further 6 hours. The solution was poured into water (500 ml.), when the very sparingly soluble sodium salt of the azine (XXVI) precipitated in finely divided form. After heating to coagulate the suspension, the sodium salt (0.63 g.) was removed by filtration. The filtrate after treatment with charcoal was acidified while still warm and the crude acid taken up in benzene. The benzene extract was washed with a little warm water, dried and passed through a column of silica (2 x 4 cm.), when brown resinous impurities were removed. The pale straw coloured crystalline acid left after removal of the solvent from the benzene eluate was washed with a little benzene/petroleum ether and finally with petroleum ether. It weighed 1.83 g. (58% of the theoretical amount). M.p. 207-208°. This product was pure enough for cyclisation. For analysis it was crystallised twice from benzene and then from 80% acetic acid and finally from benzene, giving a colourless crystalline mass of m.p. 207-208°. (Found: C, 84.9; H, 5.26. $C_{22}H_{16}O_2$ requires C, 84.6; H, 5.17%). On heating XXIII shows partial fusion in the temperature range

Insert after line 3, p. 46.

The high melting byproduct from the Wolff-Kishner reduction was crystallised repeatedly from acetic acid when it was obtained as cream coloured plates, m.p. 301-3°. (Found: C, 81.6; H, 4.46; N, 4.38; $C_{44}H_{28}O_4N_2$ requires C, 81.5; H, 4.32; N, 4.32 %).

150-170° and if heating is rapid, complete fusion may take place. The acid almost immediately solidifies as the temperature is raised and melts again at 207-208°.

(b). The keto acid was reduced with zinc dust and N potassium hydroxide solution as described by Cook[66]. The crude product was purified according to the method described under (a) except that there was no azine to remove. 9-10% of crystalline acid was recovered.

Cyclisation of 2-carboxy-1:1'-dinaphthylmethane. The procedure of Fieser and Herschberg[17,68] was followed closely. The acetate (XXIV) was a pale faun coloured mass of needles of m.p. 254-256°. Yields 85% or better. After crystallisation from benzene containing 15% of alcohol, the acetate was recovered as colourless needles, m.p. 255-256°, and was satisfactory for splitting and reduction. This compound was prepared by Cook by another method.

1:2:7:8-Dibenzanthracene (XIV). The following is a typical preparation. The dry, powdered acetate (3.6 g.) and sodium dried thiophene free benzene (60 ml.) were added to the Grignard reagent prepared from magnesium turnings (2.06 g.), n-butyl bromide (10.23 ml.) and absolute ether (50 ml.), and the mixture refluxed for one hour. The ether was allowed to distil off during this heating. The mixture while still warm was diluted

with toluene (170 ml.) and decomposed with dilute hydrochloric acid. The benzene/toluene layer was separated, washed twice with warm water, and without delay, refluxed with zinc dust (8 g.), and 2 N sodium hydroxide (200 ml.) for 7½-8 hours. The mixture was acidified with hydrochloric acid, the organic layer separated and the aqueous layer and the zinc extracted several times with benzene. The combined benzene/toluene layer was washed several times with water and the solvents removed, under reduced pressure, from the water bath. The discoloured crystalline residue was crystallised from acetic acid giving pale straw coloured needles of 1:2:7:8-dibenzanthracene, m.p. 190-191°. (2.17 g.; 73% of the theoretical amount). For a note on the further purification of XIV see below (p. 54).

1:2:7:8-Dibenz-3:4-dihydroanthracene-3:4-diol (XVI).

(a). Formation of the osmium tetroxide/pyridine complex (XV). Recrystallised 1:2:7:8-dibenzanthracene (1.64 g.; 0.0059 ml.), pure pyridine (1.44 ml.; 0.018 mol.), and osmium tetroxide (1.53 g.; 0.006 mol.) in sodium dried, thiophene free benzene (62 ml.) were mixed and allowed to stand at room temperature (8-18°) in a stoppered flask until precipitation of the complex was complete (12 days). The precipitate was collected and washed with benzene until the washings were colourless. The yield of

crude complex was practically quantitative. (The formula XV has been assumed following the results of Criegee et al[64] and of Cook and Schoental[65]).

(b). Hydrolysis of the complex. Without any preliminary purification the above complex was shaken with methylene chloride (60 ml.) and 1% potassium hydroxide solution (150 ml.) containing also 10% of mannitol, in a well stoppered flask until separation of the diol was complete. The colour of the methylene chloride layer never faded completely due presumably to the formation of traces of quinone during the shaking. The emulsified mixture was filtered immediately hydrolysis was complete. The diol was washed with water and dried in vacuo over potassium hydroxide. The colourless solid weighed 1.41 g. (76.6% of the theoretical amount). M.p. 226-228° (decomp.). From the filtrate a further 0.11 g. of discoloured diol was obtained.

1:2:7:8-Dibenz-3:4-dihydroanthracene-3:4-diacetate. The diol (XVI) possessed very poor powers of crystallisation (cf. Cook and Schoental). Attempted crystallisation led, moreover, to a deterioration in the quality of the product. It was therefore characterised by conversion to the more easily purified diacetate which was prepared as follows: the diol was mixed with excess of pyridine and acetic anhydride and after standing at room temperature 1-2 days the mixture was heated on the water bath for 20

minutes to complete the reaction. The oily, pale yellow solid which separated after diluting the acetylating mixture with ice and excess hydrochloric acid was taken up in benzene. The benzene extract was washed, dried and passed through a column of silica (2 x 4 cm.), when the yellow impurity was removed. The colourless solid left after removal of the benzene from the colourless eluate was crystallised from benzene/alcohol (1:1) giving a colourless mass of fine needles, m.p. 224.5-226°. A second crystallisation gave a product of m.p. 225-226.5°. (Found: C, 78.7; H, 5.05. $C_{26}H_{20}O_4$ requires C, 78.8; H, 5.09%)

1:2:7:8-Dibenz-3-(or 4-)-methoxyanthracene. The diol (XVI) was further characterised by conversion to 1:2:7:8-dibenz-3-(or 4-)-methoxyanthracene. The crude phenol was prepared by boiling the diol with acetic acid containing a few drops of concentrated hydrochloric acid for several minutes. After standing a few minutes the dark solution was poured into ice water and the discoloured solid collected, washed twice with water and drained rapidly since the precipitate rapidly darkened on contact with air (cf. Cook and Schoental). It was dissolved in 6 N sodium hydroxide and excess dimethyl sulphate added. The solution became warm and separation of the methyl ether soon commenced. After ¾ hour the reaction was completed by heating 20 minutes on the water bath. After diluting with water the product was

collected, washed well, dried and dissolved in warm petroleum ether (60-80°), and the solution passed through a column of alumina (2 x 5 cm.), when the coloured impurities were removed. Removal of the solvent from the colourless fluorescent eluate left a colourless crystalline residue, m.p. 180-185°, which was crystallised from petroleum ether (80-100°) giving a product of m.p. 181.5-183.5°. A second crystallisation from petroleum ether gave a product of m.p. 182.5-183.5°.
(Found: C, 89.4; H, 5.36. $C_{22}H_{16}O$ requires C, 89.2; H, 5.44%).

1:2:7:8-Dibenz-3:4-anthraquinone (XVII).

(a). To reduce the amount of sparingly soluble orange impurity (probably XXI) formed during the dichromate oxidation of the diol, attempts were made to carry out the oxidation using only the theoretical quantity of sodium dichromate. However, under these conditions only a portion of the diol was attacked. In practice it was necessary to use an excess of dichromate and boil the mixture for a few minutes. Longer heating at lower temperatures (e.g., on a boiling water bath) did not improve the yield and some diol was not attacked. The yields of XVII were never very satisfactory, but the following procedure is the most satisfactory so far tried: the diol (0.52 g.; $\frac{1}{600}$ mol.) sodium dichromate (0.5 g. in water (2 ml.) and acetic acid (75 mk.)) were mixed and heated rapidly to boiling and boiled for

8-10 minutes. The red quinone precipitated in the boiling solution as the diol dissolved. The mixture was diluted with warm water and the quinone collected and washed well with warm water. The crude product (0.44 g.) had m.p. 260-270° (decomp.). After crystallisation from tetrachloroethane it melted at 310° (decomp.) and further crystallisation did not raise the m.p. During crystallisation small amounts of an orange impurity (m.p. 340° (decomp.)), sparingly soluble in tetrachloroethane, were separated. This material has now been obtained analytically pure and is probably represented by XXI (see below). Complete separation of this impurity from XVII could not be effected by fractional crystallisation from tetrachloroethane and chloroform, but when the product crystallised twice from tetrachloroethane was sublimed cautiously at 0.3 mm. XVII sublimed first and was obtained analytically pure. Bright red needles, m.p. 310° (decomp.). (Found: C, 85.8; H, 3.86. $C_{22}H_{12}O_2$ requires C, 85.7; H, 3.93%).

(b). The diol (0.16 g.; 0.0005 mol.) and azodicarboxylic acid diethyl ester (3 g.) were mixed and heated in an oil bath at 100-110° (bath temperature) and later at 105-115° until all the diol had disappeared and no more quinone precipitated from the solution (10-12 hours). The large excess of ester was apparently necessary to act as solvent for the diol. After cooling the mixture was diluted with alcohol and the quinone

collected and washed well with alcohol. M.p. 300° (decomp.). Yield 70-80 mgms. This product was satisfactory for conversion to (2':1'-naphtha)-2:3-fluorenone. In some cases for no apparent reason the m.p. of the product was lower and crystallisation from tetrachloroethane was necessary to give a product of m.p. 310° (decomp.). The yield then was also lower.

The quinoxaline derivative of 1:2:7:8-dibenz-3:4-anthraquinone (XIX). When the quinone (XVII) was heated with excess o-phenylenediamine in acetic acid solution separation of the quinoxaline derivative began almost immediately and the reaction was completed by boiling the mixture for 15 minutes. While still warm the mixture was diluted with alcohol, the precipitate collected and washed well with alcohol. It was very sparingly soluble in most of the organic solvents available, but crystallised well from tetrachloroethane separating as tiny, yellow needles of m.p. 327-329° (decomp.) which was not raised by further crystallisation. The analyses for C, H, and N were:- C, 83.84; H, 3.92; N, 7.07%. ($C_{28}H_{16}N_2$ requires C, 88.4; H, 4.24; N, 7.37%). A sample of the analysis specimen was then examined for chlorine and gave a positive qualitative test. A Carius estimation subsequently gave Cl, 5.60%, making a total of 100.43% for the analyses. Apparently some of the solvent had been retained after drying over phosphorus pentoxide at 10 mm. and 140°C. Unfortunately at this stage no more

quinone was available for another preparation but there is little doubt that the compound described is the required quinoxaline derivative.

(2':1'-Naphtha)-2:3-fluorenone (XVIII). The purified quinone (0.28 g.) was intimately mixed with 7-8 times its weight of litharge and the mixture divided into 3 (approximately) equal lots. Each lot was introduced into an apparatus fitted for vacuum sublimation. The mixture was heated at ordinary pressure and at 260-270° (metal bath temperature), a brisk reaction spread through the mass and it became dark. After maintaining it for 1-2 minutes at this temperature vacuum was applied and the orange ketone sublimed rapidly at 0.3 mm/260-270°. The sublimate (total of 3 lots, 110 mgms.) melted at 250.5-251.5° and after crystallisation from alcohol/benzene (2:1) gave tiny orange needles, m.p. 252-253°. Further crystallisation did not raise the m.p. (Found: C, 90.0; H, 4.18. $C_{21}H_{12}O$ requires C, 90.0; H, 4.32%). When the decomposition was carried out with batches of material containing each more than about 0.1 g. quinone, the yields were lowered.

(2':1'-Naphtha)-2:3-fluorene (II). (2':1'-Naphtha)-2:3-fluorenone (75 mgms.) and 50% hydrazine hydrate solution (0.2 ml.) were heated in a sealed tube at 200-210° for 7¼-

7½ hours. The discoloured crystalline product was collected, washed well with water, dried and dissolved in warm petroleum ether (60-80°). The warm solution was passed through a column of alumina (1.2 x 4 cm.), when the coloured impurities were strongly adsorbed and the colourless, fluorescent hydrocarbon passed readily into the eluate. Removal of the solvent from the eluate left a colourless crystalline residue of m.p. 169-171.5°. Crystallisation from alcohol gave colourless, almost cubical crystals, m.p. 171.5-173°.
(Found: C, 94.8; H, 5.35. $C_{21}H_{14}$ requires C, 94.7; H, 5.30%).

Further purification of 1:2:7:8-dibenzanthracene. A sample of recrystallised 1:2:7:8-dibenzanthracene (XIV) was dissolved in hot petroleum ether (60-80°) and the solution while still warm passed through a column of alumina (B.D.H.), when small amounts of coloured impurities were strongly adsorbed, and the hydrocarbon passed through the column as a colourless, homogeneous fluorescent zone. The colourless residue left after removal of the petroleum ether from the eluate was collected and washed with a little petroleum ether, m.p. 195-196.5°. After crystallisation from ethanol/benzene (3:2) XIV had m.p. 196.5-197.5°. After three crystallisations from methanol/benzene (1:1) the m.p. was 197-198°.

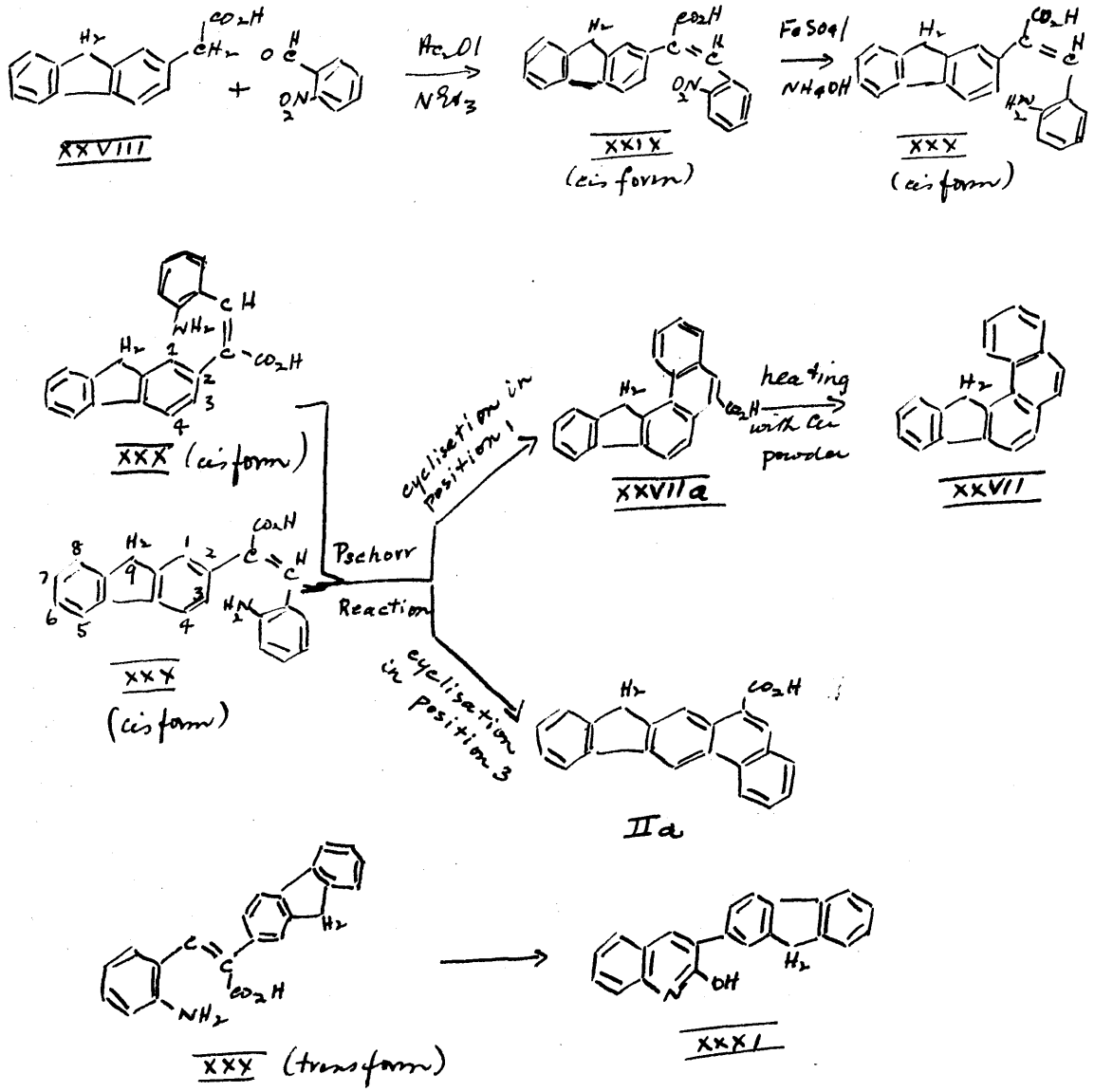
The sparingly soluble orange byproduct from the oxidation of 1:2:7:8-dibenz-3:4-anthraquinone (cf. p.47). Considerable difficulty was experienced in separating the last traces of XVII from the orange material. It was therefore boiled again with excess dichromate to oxidise the last traces of the monoquinone, and the product, recovered by pouring into water, was collected, washed, dried and extracted several times with boiling tetrachloroethane in which it was sparingly soluble. Crystallisation of the tetrachloroethane insoluble material from diethylene glycol gave tiny orange needles, melting with decomposition above 340°. (Found: C, 78.1; H, 3.16. $C_{22}H_{10}O_4$ requires C, 78.1; H, 2.98%).

The diquinoxaline derivative (XXIa). The diquinone was suspended in acetic acid and boiled gently with excess of o-phenylene diamine for 15 minutes. The separation of the diquinoxaline began immediately on warming and was soon complete. The mixture was cooled, diluted with alcohol, and the precipitate collected and washed well with alcohol. It was very sparingly soluble in all the organic solvents tried (including dioxan, tetrachloroethane and diethyleneglycol) except o-dichlorobenzene from which it separated in very small yellow crystals. M.P. > 360°. (Found: C, 84.7; H, 3.73. $C_{34}H_{18}N_4$ requires C, 84.6; H, 3.76%).

The synthesis of (1':2'-naphtha)-1:2-fluorene (XXVII).

(a). Introduction.

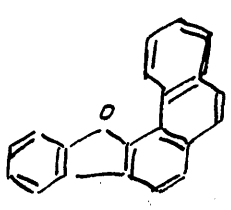
(1':2'-Naphtha)-1:2-fluorene (XXVII) was prepared according to the scheme set out below.



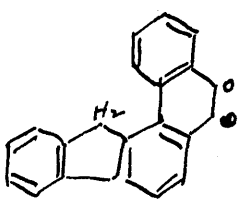
α-(2-Fluorenyl)-o-nitrocinnamic acid (XXIX) (prepared by a Perkin reaction between fluorene-2-acetic acid (XXVIII) and o-nitrobenzaldehyde) has the cis configuration, since on reduction it yields an amino acid (XXX) and not a carbostyril derivative (XXXI) which would be expected if this acid possessed the trans configuration (cf. Buchanan, Cook & Loudon[40]). The predominant formation of the cis acid is in agreement with the conclusions of Ruggli and Staub[41] and of Taylor and Hobson[113] that in the Perkin reaction between an aryl acetic acid and an a aromatic aldehyde the carboxyl group, in addition to activating the adjacent methylene group and thereby inducing the condensation, also induces a cis configuration of the 2 aryl radicals in the resulting cinnamic acid due to its stronger electronegative character compared with the aryl groups. In the present case no trans acid was isolated from the Perkin condensation.

The cyclisation of cis-α-(2-fluorenyl)-o-aminocinnamic acid (XXX) may take place in position 1 or 3, yielding either XXVIIa or IIa. It had been assumed when the synthesis was first studied with the object of preparing (2':1'-naphtha)-2:3-fluorene, that cyclisation would more probably occur in position 3. This had been shown to be the case in the cyclisation of γ-(2-fluorenyl)-butyric acid to ketotetrahydro-2:3-benzofluorene by Koelsch[28]. The cyclisation of 2-fluorenyl-

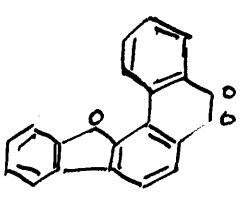
o-benzoic acid also takes place in the 3-position[63]. However, neither of these ring closures involves a Pschorr reaction, and the possibility that cyclisation would take place in the 1-position could not be excluded. The synthesis of (2':1'-naphtha)-2:3-fluorene (II) (which has already been described) by an unambiguous route was actually carried out subsequent to the Pschorr reaction described in this section. Since the acid IIa must yield II by decarboxylation and since the hydrocarbon obtained by decarboxylation of the Pschorr acid had the same molecular formula but is distinct from II, it seems that cyclisation during the Pschorr reaction must have taken place in position 1, yielding XXVIIa which must yield (1':2'-naphtha)-1:2-fluorene (XXVII) on decarboxylation. The fluorenone (XXXII) produced by oxidation of XXVII has also the same molecular formula as XVIII, but is distinct from it.



XXXII



XXXIII

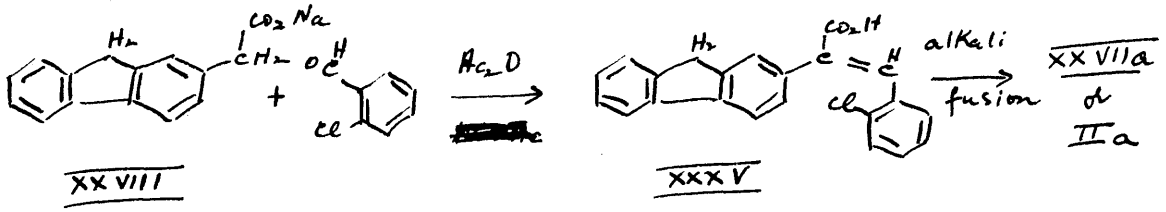


XXXIV

In carrying out the Pschorr reaction with cis-α-(2-fluorenyl)-o-aminocinnamic acid, some difficulty was encountered.

Attempts to effect diazotisation by the direct method using sulphuric acid/sodium nitrite (in presence of methanol) (cf.Cook, Buchanan & Loudon[40]) were not successful. Even on standing 20 hours much of the amino acid was recovered unchanged. It could not be separated from the diazonium salt by filtration owing to the sparing solubility of the latter. It was found possible to effect complete diazotisation by addition of amyl nitrite to a solution of the amino acid in alcohol acidified with concentrated hydrochloric acid (cf. 41-45). With sulphuric acid the diazotisation was incomplete. Ring closure was effected by addition of freshly prepared copper powder to the suspension of the diazonium salt in alcohol without preliminary dilution with water.

An alternative procedure to the above synthesis was also explored.



XXVIII XXXV XXVIIa or IIa

Following a method due to Hewett[46] o-chlorobenzaldehyde was condensed with fluorene-2-acetic acid (as its sodium salt) in a Perkin reaction to give cis-α-(2-fluorenyl)-o-chlorocinnamic acid. Attempts to effect ring closure of this acid by alkali fusion were not successful. Temperatures sufficiently

high to cause dehalogenation of the material led to widespread decomposition and no pure product was isolated from the reaction mixture.

(b) Experimental.

2-Acetylfluorene was prepared on three times the scale given by Bachmann and Sheehan[38]. The procedure was that given by these authors except that it was found better to keep the reaction mixture at 5-10° during the addition of the fluorene and to stir for 3 hours at 0-10° before removing the ice bath. It was also found necessary to use an additional 50-100 ml. of nitrobenzene in excess of the proportionate amount given by these authors. Vacuum sublimation of the crude product was found more convenient than vacuum distillation. The product crystallised from alcohol (charcoal) rather than from acetone in which it was very soluble, was obtained as colourless crystals, m.p. 127-128°.

Fluorene-2-acetic acid (XXVIII). (a). The preparation of this compound from 2-acetylfluorene by a Willgerodt reaction is described by Bachmann and Sheehan[38]. The alternative preparation[38] by an Arndt-Eistert reaction from fluorene-2-carboxylic acid did not seem attractive. Using the proportions of reactants given by Bachmann and Sheehan, the fluorene-2-acetic acid was found to be contaminated with considerable

quantities of fluorene-2-carboxylic acid. The latter acid was isolated and converted to its methyl ester using ethereal diazomethane, m.p., after crystallisation from methanol, 125-126° (cf. Fortner[47]). The discrepancy is probably due to the variable concentration of the ammonium polysulphide solution. Bachmann and Sheehan prepared their reagent according to the directions of Fieser and Kilmer[44], i.e., by saturating concentrated ammonia with hydrogen sulphide and then stirring into this solution 1/10 of its weight of sulphur. In the present investigation also the ammonium sulphide reagent was first prepared by Fieser's and Kilmer's method. Using this reagent the following proportions of reactants gave satisfactory results, viz., 3 g. 2-acetylfluorene, 9 ml. polyammonium sulphide solution and 15 ml. of dioxan. Increase of the proportion of polysulphide much beyond this limit led to the formation of fluorene-2-carboxylic acid. With too low proportions of the polysulphide reagent, large quantities of neutral products were formed, and the quality of the acid product was inferior. These findings are in general agreement with Willgerodt's original observations on this type of reaction[50-52], i.e., he found that too large an excess of the polysulphide reagent caused degradation of the side chain to the carboxylic acid with one carbon atom less, while too small a proportion of the

reagent led to the production of neutral products. Similar observations have been made by later workers[44,48,49].

After many experiments had been completed, a number of papers dealing with the Willgerodt reaction appeared. In particular, De Tar and Carmack[48] found that a more reproducible sulphide reagent is prepared by suspending in concentrated ammonia 1/10 of its weight of sulphur and passing in hydrogen sulphide until the sulphur just dissolves. Later preparations have been carried out using this reagent. It has been found necessary to increase the proportion of reagent to 12.5 ml. for 3 g. of 2-acetylfluorene, and 15 ml. of dioxan to obtain the same yields as previously. The time of heating (at 160-170°) has also been reduced from 10 to 8 hours. Further reduction of the heating time appears to reduce the yield, but this point needs further investigation. The procedure for working up the product has also been varied and the following method has been found to be the most satisfactory.

2-Acetylfluorene (3 g.), ammonium sulphide reagent (12.5 ml.), and dioxan (peroxide free; 15-17 ml.) were heated in a small stainless steel autoclave at 160-170° for 8 hours and left to cool overnight. The contents were washed out with alcohol and evaporated to dryness on the water bath. The crude amide was then dissolved in acetic acid (40 ml.) and concentrated hydrochloric acid (12 ml.), the mixture refluxed for 7 hours,

and poured into water. The precipitate was collected, washed and dissolved in hot dilute sodium carbonate solution (250-300 ml.) and filtered (filter cel was added to improve filtration). The crude acid recovered by acidification of the filtrate was crystallised from 50% alcohol (charcoal), when it was obtained as a colourless, crystalline mass, m.p. 175-177°. Yields, 1.8-2.0 g. Occasionally, for no apparent reason, an experiment gave a lower yield accompanied by some tar formation, although the same conditions and reagents from the same batch were used.

It is stated[49b] that the Kindler modification of the Willgerodt reaction is not successful with 2-acetylfluorene (or with other compounds containing reactive methylene groups as in fluorene) and no attempt was made to investigate it. In view of the experience with this reaction it would seem desirable to run a small scale experiment to test each new batch of ammonium sulphide reagent.

Note on melting point of fluorene-2-acetic acid. When the crystallised fluorene-2-acetic acid was sublimed at 3 x 10^{-3} mm. and the sublimate crystallised from benzene, the m.p. obtained was 183°. Bachmann and Sheehan reported 186-187° (after vacuum sublimation and crystallisation) and v. Braun and Engel[39] 178° for a product prepared by hydrolysis of 2-fluorenyl acetonitrile and subsequent crystallisation from alcohol.

(b). At the stage of these investigations when the Willgerodt reaction was being used to prepare fluorene-2-acetic acid, only a small autoclave was available, consequently limiting the scale of experiments. In efforts to obtain larger quantities of this acid, its preparation by way of the 2-chloromethyl compound and hydrolysis of the corresponding nitrile was investigated. The yields of fluorene-2-acetic acid so obtained are poor and the method is inferior to the Willgerodt reaction when suitable apparatus is available for the latter reaction. Since, however, fluorene-2-acetic acid does not seem to have been prepared previously via the chloromethylation reaction, the results are reported. 2-Chloromethylfluorene and 2-fluorenylacetonitrile have been prepared by v. Braun and Engel[39], but the preparation of the former from 2-aminofluorene via the nitrile, 2-fluorenylmethylamine and 2-fluorenylcarbinol is too laborious for a large scale method. The chloromethylation of fluorene was next investigated. Dziewonski and Panek[114] state that methylal, fluorene and chloroform in the presence of phosphorus pentoxide give 2:2'-difluorenylmethane (m.p. 201-202°). No mention of the isolation of the chloromethyl compound is made in the abstract. In the present investigation the chloromethylation of fluorene has been studied under a variety of conditions, but the yields of chloromethyl compound

were always poor due to the ease with which it polymerises (cf. v. Braun and Engel). Attempts to use the procedure described in Organic Syntheses for the preparation of α-chloromethyl naphthalene and various modifications thereof were very unsatisfactory. Slightly better results were obtained by use of paraformaldehyde solution in acetic acid saturated with hydrogen chloride, with or without the addition of zinc chloride, as chloromethylating agent. When the reaction was allowed to proceed until all the fluorene was consumed, practically all the chloromethyl compound was polymerised. It was found necessary to stop the reaction when much unchanged fluorene was still present. Separation of the chloromethyl compound from the fluorene was not practicable, but the mixture of the two was treated with excess concentrated potassium cyanide solution and acetone. The crude nitrile thereby obtained was not purified but hydrolysed. The resulting fluorene-2-acetic acid was readily separated from the accompanying neutral impurities. After a number of experiments it was found better not to heat the chloromethylating mixture but to add a little zinc chloride as catalyst and allow it to stand several days at room temperature. The details of a typical experiment are: dry hydrogen chloride was passed into a mixture of paraformaldehyde (6 g.; 0.2 mol.) and glacial acetic acid (200 ml.) until

all the paraformaldehyde had dissolved. Fluorene (13.3 g.; 0.08 mol.) and powdered zinc chloride (0.5 g.) were then added and the passage of hydrogen chloride continued for ½ hour longer. The flask was then stoppered and allowed to stand at room temperature for 4½-5 days. The mixture was diluted with ice water, the precipitate collected, washed with water, with dilute sodium carbonate solution until the washings were alkaline, and again with water, and drained well. The product was treated immediately with excess concentrated potassium cyanide solution and sufficient acetone to dissolve it and the mixture refluxed for 2½-3 hours. After removal of the acetone the oily residue was diluted with water and the resulting solid collected, washed well and hydrolysed with a mixture of acetic acid/concentrated hydrochloric acid (3:1). The crude product obtained after diluting the hydrolysis mixture with water was digested with dilute sodium carbonate solution and filtered. If necessary, the filtrate was heated with charcoal and again filtered. The colourless fluorene-2-acetic acid recovered by acidification of the filtrate had m.p. 178-180° and weighed 1.9 g. Sublimation of the alkali insoluble fraction (at 0.4 mm.) gave 7.8 g. of practically pure fluorene. Yield of the fluorene-2-acetic acid based on the fluorene used is 25%. If the residue left after sublimation of the fluorene is sublimed at 1.5×10^{-2} mm./225-240° (temperature of heating

jacket) a crystalline sublimate is obtained which after crystallising from acetic acid and twice from petroleum ether had m.p. 201-202°. (Found: C, 94.1; H, 5.81. Calculated for $C_{27}H_{20}$, C, 94.2; H, 5.85%). This is evidently the 2:2'-difluorenylmethane described by Dziewonski and Panek[114].

Cis-α-(2-Fluorenyl)-o-nitrocinnamic acid (XXIX). The sodium salt of fluorene-2-acetic acid was employed in the first Perkin condensations, but in later experiments the triethylamine salt was used since it gave better yields[53,54]. The following procedure was finally adopted. Fluorene-2-acetic acid (dried at 110°; 5.6 g., 1/40 mol.), o-nitrobenzaldehyde (4 g., ca. 5% excess), triethylamine (2.52 g., 3.45 ml., 1/40 mol., dried over potassium hydroxide), and acetic anhydride (analar., 30 ml.) were mixed and heated at 85-95° (oil bath temperature) for 11-11.5 hours. The clear, pale brown solution was poured, while still warm, into 250 ml. of cold water with vigorous stirring and let stand 12 hours or longer. The mixture was then heated on the water bath for 1-2 hours until the oily solid had completely solidified, cooled, filtered, washed and the still damp residue dissolved in ca. 230 ml. of hot benzene. The solution was cooled and filtered to remove a little trans-o-nitrocinnamic acid, and then extracted repeatedly with dilute sodium carbonate solution until practically all acidic material

was removed. The combined alkaline extracts were heated on the water bath with a little charcoal, filtered and the crude cis-α-(2-fluorenyl)-o-nitrocinnamic acid was recovered from the filtrate by acidification with concentrated hydrochloric acid. (Yield of the crude acid 8.75 g., 98.5%). Crystallised from 50% acetic acid, then from 50% alcohol and finally from benzene/petroleum ether (80-100°), it gave bright yellow needles, m.p. 215-216° (probably decomp.). (Found: C, 74.2; H, 4.32; N, 3.88. $C_{22}H_{15}O_4N$ requires C, 73.9; H, 4.23; N, 3.92%).

Note. In this Perkin reaction a temperature of 85-95° gave higher yields than one of 90-100° (cf. Amstutz and Spitzmiller[85]). When the sodium salt was used heating for 7 hours at 130-140° or 8 hours at 115-125° gave yields which were much smaller - ca. 60% - than when the triethylamine salt was used.

cis-α-(2-Fluorenyl)-o-aminocinnamic acid (XIV). Following the usual procedure for the reduction of α-arylsubstituted-o-nitrocinnamic acids (cf. 40,42,43,44) (XIV) was reduced with ferrous sulphate and ammonia. In most experiments the crude nitro acid from the Perkin reaction was used without further purification since the same product was obtained as from the purified acid. A typical experiment was as follows: to 22 g. of ferrous sulphate ($FeSO_4.7H_2O$) dissolved in 50 ml. of warm water

there was added with shaking 2.7 g. of finely powdered crude cis-α-(2-fluorenyl)-o-nitrocinnamic acid in 100 ml. of water and 140 ml. of concentrated ammonia, and the mixture was heated on the water bath for nearly 2 hours. After dilution with hot water and addition of charcoal, the mixture was boiled for a few minutes and filtered. The residues were washed repeatedly with hot 1% ammonia until they were practically free from amino acid. This washing was always tedious because of the sparing solubility of the ammonium salt of the amino acid. The combined filtrate and washings were acidified with acetic acid, when the bright yellow amino acid separated. It had m.p. 217.5-219.5°. Yield 1.9 g. (77% of the theoretical amount). It was further purified by dissolving in hot dilute sodium carbonate solution and heating on the water bath with charcoal. The acid recovered from the filtrate by acidification with acetic acid had m.p. 217-219° and is sufficiently pure for cyclisation. For analysis it was crystallised first from alcohol giving yellow needles, m.p. 217-219° (probable decomp.) which on crystallising twice from benzene had m.p. 217.5-219.5° (probable decomp.). (Found: C, 80.9; H, 5.05; N, 4.14. $C_{22}H_{17}O_2N$ requires C, 80.7; H, 5.25; N, 4.28%).

This acid forms sparingly soluble sodium and ammonium salts. The reduction has also been carried out on a larger scale, but the yields were somewhat lower.

Cyclisation of cis-α-(2-fluorenyl)-o-aminocinnamic acid.

(a). Diazotisation methods using sodium nitrite and an aqueous suspension of a salt of the amino acid gave always incomplete diazotisation. Owing to its sparing solubility it was not possible to separate the diazonium salt from the unchanged amino acid by filtration.

(b). For complete diazotisation by the amyl nitrite method it was necessary to use HCl in place of sulphuric acid and carry out the reaction at room temperature (ca. 20°). A typical experiment was as follows: cis-α-(2-fluorenyl)-o-aminocinnamic acid (1.58 g.) was dissolved in warm alcohol (250 ml.) and cooled to 10-15°. (It was necessary to use sufficient alcohol to dissolve the amino acid completely at room temperature). Concentrated hydrochloric acid (32 ml.) was poured in rapidly, the mixture shaken and redistilled isoamyl nitrite (3.5 ml.) added without delay in one portion. If the temperature had risen above 20° the mixture was cooled to 20° and let stand at this temperature for 1.5 hours. The separation of the yellow diazonium salt commenced after a few minutes. In the above procedure it is essential to add the nitrite before the separation of the hydrochloride begins or diazotisation will be incomplete.

To decompose the diazonium salt freshly prepared copper powder was added and the mixture shaken at room temperature

until a negative coupling test was obtained with β-naphthol. The cyclised acid began to precipitate towards the end of the reaction. The temperature usually rose several degrees during the decomposition but was never allowed to exceed 30°.

Note. The copper powder used was prepared by the method of Gattermann[91] and stored under water. Specimens which had turned dark gave lower yields. With amounts of amino acid larger than the above quantity the yields also decrease. It also seems disadvantageous to decrease appreciably the large proportion of alcohol. A dioxan/alcohol solution may be superior but no dioxan (cf. 42,43,45) was available. Addition of excess of sodium hypophosphite solution (cf. 41) during the decomposition did not seem an advantage. In the absence of copper powder the hypophosphite did not effect complete decomposition. In one experiment copper powder was omitted and the acid suspension of the diazonium salt neutralised with sodium carbonate solution (cf. 40). The mixture was allowed to stand at room temperature until the coupling test with β-naphthol was negative (< one hour). From the reaction mixture a crude substance was isolated which could not be purified completely but by its behaviour was apparently XXVIIa.

The reaction mixture was diluted to 1200 ml. with cold water and the precipitate collected and washed. It is

advisable not to heat the reaction mixture during any of these procedures, as the formation of dark coloured byproducts is thereby practically avoided. The crude acid was heated with 500 ml. of dilute sodium carbonate solution in which it was almost completely soluble, digested with a little charcoal and the solution filtered. The cream coloured acid was crystallised from acetic acid to give a cream coloured nicely crystalline product of m.p. 250-251° weighing 0.91 g. (60.6% of the theoretical amount). A sodium fusion test for nitrogen and chlorine on this material was negative.

For analysis this acid was crystallised twice more from acetic acid without raising the m.p. and finally from benzene containing 10% of alcohol, when it was obtained as a cream coloured crystalline mass of needles m.p. 251-252.5° (decomp.). Considerable sublimation takes place below the m.p. of this acid. (Found: C, 85.0; H, 4.40. $C_{22}H_{14}O_2$ requires C, 85.2; H, 4.55%).

The acid is sparingly soluble in benzene, readily soluble in alcohol and acetone, moderately soluble in acetic acid. From the crude reaction product there was also isolated in small amounts an acid of m.p. 269-271°. It gave an empirical formula of $C_{24}H_{19}O_6$ on analysis and was in too small an amount to investigate further. (Found: C, 71.4; H, 4.76%).

(1':2'-Naphtha)-1:2-fluorene (XXVII). (a) Heating a quinoline solution of the Pschorr acid with copper powder for 3 hours caused practically complete decarboxylation, but no pure compound could be isolated from the crude neutral product. (b) (XXVIIa)(crystallised from acetic acid, m.p. 250-251°) was mixed intimately with 1-2 times its weight of dry copper powder and heated at ordinary pressure at 260-280° in a metal bath for several minutes. The product was then sublimed under reduced pressure (0.2-0.4 mm. with a bath temperature of 300-320°). The decarboxylation procedure should be carried out on a small scale, preferably with each batch containing not more than 0.2 g. of acid. The yields are always poor (e.g., in a favourable case 0.85 g. of XXVIIa yielded 0.15 g. (20%) of purified (1':2'-naphtha)-1:2-fluorene).

The sublimate was a deep cream crystalline mass encrusted with a thin layer of red material (probably a mixture of the quinone (XXXIII) and the ketone (XXXII) (p. 58)). It was digested with 1% sodium hydroxide solution on the water bath, filtered hot and washed well with hot water. Acidification of the filtrate precipitated small amounts of unchanged acid. The alkali insoluble residue was dried and dissolved in petroleum ether (60-80°), and passed through a column of alumina (10 x 2 cm.; B.D.H.). The red impurities were more strongly adsorbed than the hydrocarbon which was slowly eluted

by petroleum ether as a uniform, colourless band (strongly fluorescent in ultra violet light). Elution may be completed by addition of 10 and finally 20% of benzene to the petroleum ether. Alternatively the column may be cut after development with petroleum ether and the hydrocarbon eluted with chloroform. Evaporation of the petroleum ether eluate left a faintly yellow crystalline product which, crystallised from petroleum ether (60-80°), gave colourless crystals (plates, m.p. 158.5-159.5°). (Found: C, 94.7; H, 5.23. $C_{21}H_{14}$ requires C, 94.7; H, 5.30%)

(XXVII) may also be crystallised from alcohol, when it separates as a mixture of needles and plates. The m.p. observed under the microscope showed that the needles melted several degrees below the plate forms. The melt allowed to cool deposited only plate forms of the above recorded m.p. Another sample of the same batch of material crystallised only from petroleum gave only the plate forms. The needles uncontaminated by plates were not isolated. (XXVII) is very soluble in benzene and chloroform, moderably soluble in alcohol and petroleum ether.

After removal of XXVII the red material was eluted with chloroform, when it divided into two main bands of which the most strongly adsorbed - a bright yellow band - left a yellow crystalline solid (m.p. 237.5-242°) on evaporation of the

solvent. There was not sufficient of this material for complete purification, but it is probably an impure specimen of the substance of m.p. 243-244° isolated from the oxidation products of XXVII (see below).

Oxidation of (1':2'-naphtha)-1:2-fluorene. A sample of the hydrocarbon was dissolved in acetic acid and to the boiling solution excess sodium dichromate was added, the mixture refluxed for 15 minutes, and poured into water. The yellow precipitate was extracted with benzene. The extract was washed with water, then with aqueous sodium carbonate until the washings were alkaline, and again with water. After drying over sodium sulphate the solution was passed through a column of alumina (2 x 8 cm.; B.D.H.). The first eluate (yellow) passed through easily and on evaporation left a yellow orange crystalline residue (slightly sticky). Crystallised from benzene in which it was readily soluble, and then from alcohol, it gave a homogeneous mass of orange needles, m.p. 152-153°. (Found: C, 90.0; H, 4.39. $C_{21}H_{12}O$ requires C, 90.0; H, 4.32%). The analysis agrees with (1':2'-naphtha)-1:2-fluorenone (XXXII).

A more strongly adsorbed red band was eluted with chloroform. On evaporation of the solvent a yellow crystalline residue of m.p. 238-240° (decomp.) remained. It was

crystallised from benzene in which it was sparingly soluble, giving a homogeneous mass of yellow plates, m.p. 243-244° (decomp.). There was not sufficient material for further purification. (Found: C, 84.4; H, 4.03. $C_{21}H_{12}O_2$ requires C, 85.1; H, 4.08%).

The product is probably (XXXIII). Contamination with a little (XXXIV) would account for the low carbon analysis, and the two quinones would probably not be separated readily by chromatography.

Attempts to prepare a picrate and a 1:3:5-trinitrobenzene derivative of (XXVII) failed.

Note. Further investigation of the decarboxylation of the Pschorr acid.

(c). The acid was mixed with finely powdered soft glass and the mixture treated similarly to the case using copper powder. The acid sublimed unchanged.

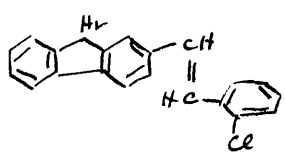
(d). An acetic anhydride solution of (XXVIIa) was refluxed with copper powder. No crystalline material could be isolated from the product. Only a very small amount of material was available from this test and the results were not conclusive.

(e). A small amount of (XXVIIa) was converted to its silver salt by standard procedures. The dry, finely powdered silver salt (cf. 56) was added in portions to boiling quinoline

(synthetic, dried over potassium hydroxide) (the flask was heated in a metal bath). After refluxing 0.5 hours the mixture was cooled, diluted with benzene, extracted repeatedly with dilute hydrochloric acid, washed with water and then with sodium hydroxide solution. Acidification of the alkaline extract gave only traces of the unchanged acid. The benzene layer after drying over calcium chloride was passed through a column of alumina (B.D.H.). Evaporation of the filtrate left a crude sample of (XXVII). It was contaminated with a red material, presumably a mixture of (XXXII) and (XXXIII). Not sufficient of the acid was available at this stage to allow a quantitative comparison of the yields by this method with those from (b) (p.73).

cis- α-(2-fluorenyl)-o-chlorocinnamic acid (XXXV). Sodium 2-fluorenyl acetate (1.35 g.; 0.0055 mol.), o-chlorobenzaldehyde (0.77 g.; 0.0055 mol.) and acetic anhydride (7.5 ml.) were mixed and heated in an oil bath at 130-140° (oil bath temperature) for 8 hours. The product, while still warm, was poured into cold water (100 ml.) with vigorous stirring, and let stand 12 hours or longer. The mixture was then heated on the water bath until the oily solid had completely solidified (1-2 hours), filtered hot, and the insoluble residue washed with hot water. On cooling a little crystalline material separated

from the filtrate. This was shown to be mainly trans-o-chlorocinnamic acid and was rejected. The brown insoluble residue was digested with hot dilute sodium carbonate solution on the water bath until no more solid dissolved and filtered hot. The crude acid recovered by acidification of the filtrate was crystallised repeatedly from benzene, once from aqueous acetone and again from benzene, giving a homogeneous mass of colourless needles, m.p. 229-231° (slight decomp.). (Found: C, 76.1; H, 4.36; Cl, 10.3. $C_{22}H_{15}O_2Cl$ requires C, 76.2; H, 4.36; Cl, 10.23%). This material is presumably the cis isomer. It is readily soluble in alcohol, acetone, acetic acid and benzene, and less soluble in petroleum ether. The alkali insoluble material was dissolved in benzene and the solution filtered to remove traces of the sodium salt of cis-α-(2-fluorenyl)-o-chlorocinnamic acid. Removal of the benzene left an oil which solidified on treatment with alcohol. Crystallised from alcohol (charcoal) it gave light yellow crystals, m.p. 137.5-138.5°. Crystallised again from petroleum ether (80-100°) it gave a pale yellow crystalline mass of m.p. 138-139°. (Found: C, 83.4; H, 4.84; Cl, 11.24. $C_{21}H_{15}Cl$ requires C, 83.3; H, 4.99; Cl, 11.71%). The compound is presumably trans-α-(2-fluorenyl)-β-(o-chlorophenyl)-ethylene (XXXVI).



XXXVI

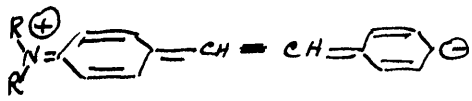
Part II.

Synthesis of α-(2-fluorenyl)-β-aryl-ethylenes.

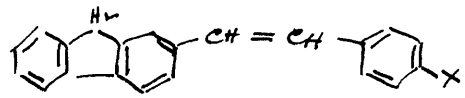
Synthesis of α-(2-fluorenyl)-β-arylethylenes.

a). Introduction.

It has already been stated in the General Introduction that certain basically substituted αβ-diarylethylenes possess both carcinogenic and tumour inhibitory properties (the degree of the latter effect depending on the protein content of the diet of the experimental animal). In a recent report[115c] the data at present available on the relation between chemical structure and tumour inhibitory and carcinogenic activity in this series of compounds are summarised. A basic group in the ortho or para position of an αβ-diarylethylene possessing an unsubstituted ethylenic bridge appear to be essential features. One free para position seems necessary except in certain cases (no specific examples of this are given in the report). An increase in the size of certain substituents leads to a decrease in activity. Finally only the trans isomers of these αβ-diarylethylenes show the biological properties in question. To account for these observations it has been suggested as a provisional hypothesis that "one of the features required for biological effectiveness is an unbroken conjugation of the amino group with both nuclei, which enables the compound to assume a dipolar quinonoid form (A)."



A

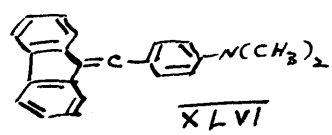


B

X = H, NO_2, Cℓ, OCH_3, NH_2, $NHOCCH_3$, $N(CH_3)_2$

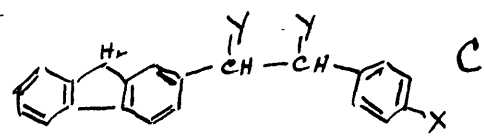
A coplanar arrangement of the aryl nuclei is also essential for the existence of form A, and this is obtained only in the trans forms of the $\alpha\beta$-diarylethylenes. In the cis forms the aryl groups cannot assume a coplanar configuration because of steric factors, and the resonance energy is greatly reduced.

In the present work the preparation of a series of compounds of the general formula B was undertaken with the object of submitting them to biological examination. The substituents in the para position were not limited to basic groups since it seemed of interest to test the general hypothesis in this respect. As far as it is known no $\alpha\beta$-diarylethylenes with one of the aryl groups a 2-fluorenyl radical have been prepared and examined for tumour inhibitory properties. The 9-fluorenyl derivative (XLVI) has been reported to be active[84].



XLVI

Since it has been reported that certain $\alpha\beta$-diarylethylamines[127] possess tumour inhibitory action



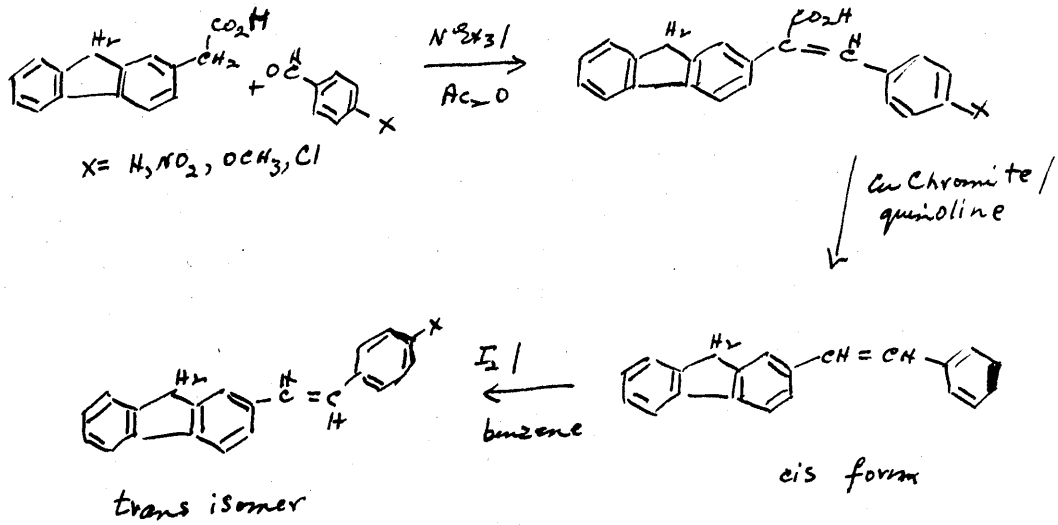
C

X = H, NO_2, OCH_3 etc.

Y = H or NH_2

the preparation of compounds of the general formula C was investigated. Only a preliminary exploration has been made in this section partly through lack of time and partly due to the unattractive properties of some of the intermediate compounds. A description of the compounds obtained is given in the experimental section.

As regards the preparation of the type B compounds an approach through the Perkin reaction was first investigated.



The Perkin reaction gave satisfactory results in all the cases indicated, and where a comparison was carried out triethylamine as catalyst gave better yields than sodium or potassium acetate. For X = H, OCH_3, Cl decarboxylation of the cis-α-(2-fluorenyl)-cinnamic acids gave fair yields of the cis-α-(2-fluorenyl)-β-(p-substituted-phenyl)-ethylenes which could be smoothly isomerised to their trans isomers by heating with iodine in

benzene. In the case of the nitro compound, however, the decarboxylation gave very poor yields of the cis isomer. This also isomerised smoothly to its trans isomer. Reduction of this trans-α-(2-fluorenyl)-β-(p-nitrophenyl)-ethylene (XXXVIII) with stannous chloride gave the corresponding amino compound which was purified as its N-acetyl derivative. However, the amount of nitro compound available by the above method was not sufficient to allow the preparation of a sample of the N-acetyl derivative for biological testing.

Another route to trans-α-(2-fluorenyl)-β-(p-nitrophenyl)-ethylene was obtained by the following series of reactions. p-Nitrophenylacetyl chloride was condensed with fluorene under Friedel-Crafts conditions and the resulting 2-fluorenyl-p-nitrobenzyl-ketone (XXXIX) was reduced by aluminium isopropoxide to the corresponding carbinol (XXXIXa). This was dehydrated with acetic anhydride containing hydrogen chloride, when (XXXVIII) was obtained in small quantity.

Trans-α-(2-fluorenyl)-β-(phenyl)-ethylene (XXXVII) and α-(2-fluorenyl)-β-(p-nitrophenyl)-ethylene (XXXVIII) were also prepared in very small yields by coupling diazotised 2-aminofluorene with cinnamic and p-nitrocinnamic acids respectively, according to the method of Meerwein, Büchner and van Emster[58] and of Bergmann and coworkers[59]. Further description of these experiments is included in the experimental section. The

mechanism of this interesting reaction is still a matter of dispute but some evidence supports the free radical mechanism indicated below[cf.118,121].

$$Ar'N_2Cl \rightleftharpoons [Ar'N_2]^+ + Cl^- \qquad [\text{In present cases } Ar' = \text{(naphthyl)}, Ar = C_6H_5 \text{ or } C_6H_4.NO_2]$$

$$[Ar'N_2]^+ + CH_3.CO.O^- \rightleftharpoons Ar'N_2OCOCH_3 \xrightleftharpoons[\text{acetone}]{aq} Ar'^{*} + N_2 + CH_3.CO.O^{*}$$

(a) $$Ar.CH{=}CH.CO_2H + Ar'^{*} \longrightarrow Ar\overset{*}{C}H : \underset{Ar'}{\overset{H}{C}}CO_2H \xrightarrow{Cu^{++}} Ar\overset{+}{C}H : \underset{Ar'}{\overset{H}{C}}CO_2H + Cu^{+}$$

I

$$\xrightarrow{Cl^-} Ar.CHCl.\underset{Ar'}{CH}.CO_2H \longrightarrow HCl + CO_2 + ArCH{=}CHAr'$$

or $$Ar\overset{+}{C}H : \underset{Ar'}{\overset{H}{C}}CO_2H \longrightarrow ArCH{=}CHAr' + H^+ + CO_2$$

$$Cu^{+} + CH_3.CO.O^{*} \longrightarrow Cu^{++} + CH_3.CO.O^{-}$$

The free aryl radical Ar' may add to either the α or β carbon atom of the cinnamic acid giving I or II. However, the product finally isolated corresponds to addition of Ar' to the α carbon atom. It has been pointed out[118] that the free radical I will be more stable than the alternative free radical II since resonance in the more symmetrical

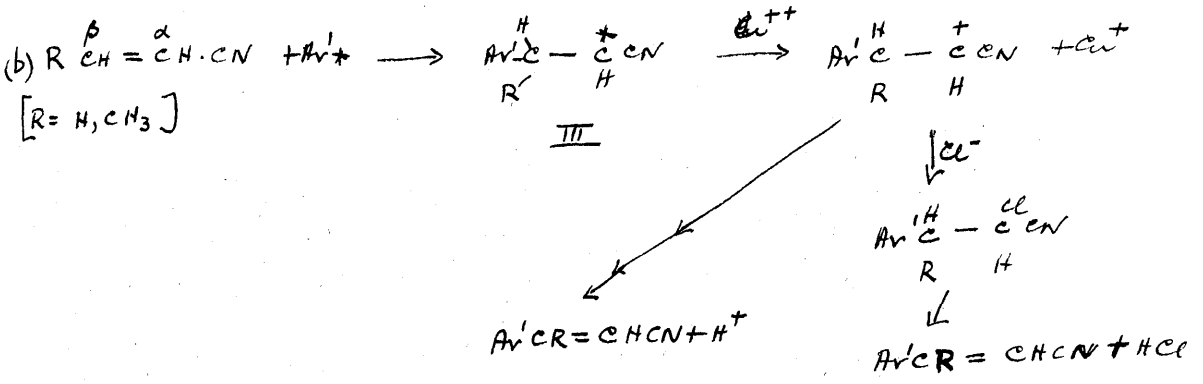
$$Ar\overset{*}{C}H - \underset{Ar'}{\overset{CO_2H}{CH}}$$

I

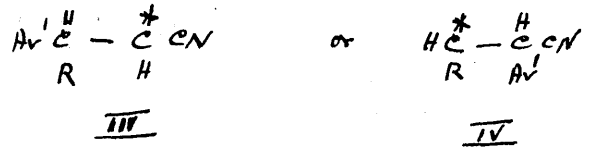
$$\underset{Ar'}{\overset{Ar}{>}}CH - \overset{*}{C}H\,CO_2H$$

II

system represented by I will be greater than the resonance in system II. This idea receives further support from the observation that in the acrylic and crotonic acid series addition of Ar' takes place at the β-carbon atom. Thus:



The possible intermediate radicals are:



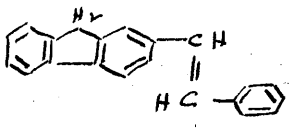
Of these III can be stabilised by resonance of the odd electron with the CN group, but in IV stabilisation by resonance with H or CH_3 is not possible. Hence it is assumed that III will have the lower energy content and, therefore, will presumably be more easily formed. The free radical mechanism also explains the roles of the acetone, sodium acetate and cupric ions. Cuprous ions are said to have no catalytic effect in the Meerwein reaction. In the case of diazonium compounds there is independent evidence[121,126] that in solvents such as buffered

aqueous acetone some dissociation to free radicals takes place. Waters has shown that a solution of a diazonium chloride in aqueous acetone (free acid neutralised by chalk) attacks copper, mercury, silver, gold, etc. to give metallic chlorides and even organo-metallic compounds, while in the absence of the acetone the corresponding reactions do not occur.

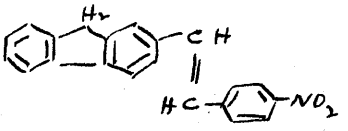
Since the experiments described in this report have been carried out it has been claimed by Indian workers[125] that in the Meerwein coupling of aryl diazonium chlorides with maleic acid acetone is not essential to the reaction. No experiments on the coupling reaction with cinnamic acids were reported.

For the preparation of α-(2-fluorenyl)-β-(p-dimethylaminophenyl)-ethylene (XLIV) fluorene-2-acetic acid was heated with p-dimethylaminobenzaldehyde in the presence of piperidine (cf. for example 128). Considerable amounts of resinous by-products were also formed. The corresponding α-(2-fluorenyl)-p-dimethylaminocinnamic acid was not isolated from the reaction mixture. The ethylene obtained is presumed to have the trans configuration because of its high melting point and from analogy with the products of similar reactions (cf. for example 129,128). Attempts were made to prepare α-(2-fluorenyl)-p-dimethylaminocinnamic acid by methylation of α-(2-fluorenyl)-p-aminocinnamic acid under various conditions, but a pure product was not obtained, and this route to the desired ethylene

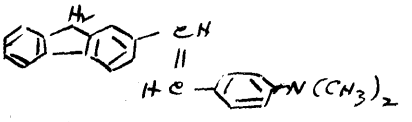
by subsequent decarboxylation of the required cinnamic acid was abandoned.



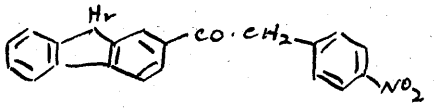
XXXVII



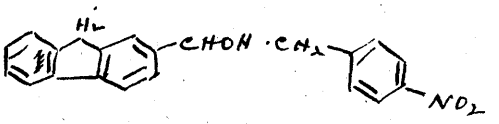
XXXVIII



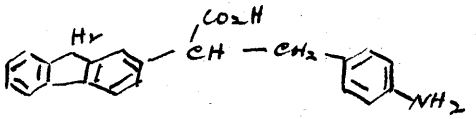
XLIV



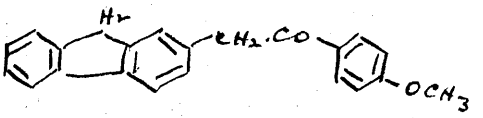
XXXIX



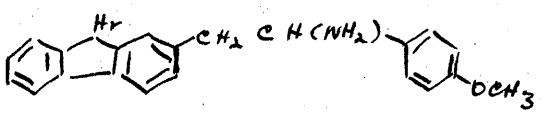
XXXIXa



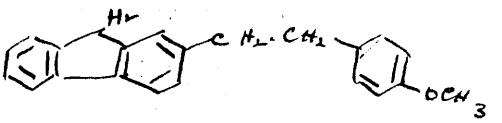
XL



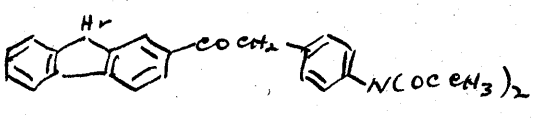
XLI



XLII



XLIII



XLV

Since the cis or trans configuration of the $\alpha\beta$ -diaryl-ethylenes is of importance in connection with their biological properties, the evidence for the configurations of the compounds prepared is briefly described. As already mentioned in a previous section (p.57) the α-arylcinnamic acids prepared by Oglialoro's modification of the Perkin reaction have exclusively or predominantly the cis configuration (i.e., the aryl groups are cis to one another). When the cis acids are submitted to decarboxylation with quinoline and copper chromite (usually the most effective method available) there is generally little isomerisation and the resulting stilbenes have predominantly the cis configuration.[41,113,116] Chromatography is probably the most convenient method for separating the small amount of the trans isomer and any other impurities from the cis form[116]. The trans form seems invariably to be the more strongly adsorbed (alumina as adsorbent[116]). In the present work the isomers were all fluorescent and the zones could be distinguished under ultra violet light. Using this guide, small amounts of trans-α-(2-fluorenyl)-β-(phenyl)-ethylene (XXXVII) were separated from the cis isomer, when the decarboxylation product from the pure cis-α-(2-fluorenyl)-cinnamic acid was chromatographed on alumina. Similar separations were effected with the other pairs of isomers prepared by decarboxylation of the corresponding

cis-arylcinnamic acids. When the isomers are colourless or non-fluorescent it is usual to search for an indicator which will show different colours with the two isomers[116]. If the chromatography is carried out at room temperature there is, as a rule, no isomerisation on the column.

In the case of the Perkin reaction it is sometimes possible to isolate a stilbene as well as the α-arylcinnamic acid from the reaction mixture. The stilbenes so isolated seem always to have the trans configuration[58,59,122]. Kuhn and Winterstein's modification of the Perkin synthesis using litharge as catalyst often favours production of the stilbene at the expense of the cinnamic acid[59,122,117]. However, when this reaction was applied to fluorene-2-acetic acid and p-nitrobenzaldehyde only cis-α-(2-fluorenyl)-p-nitrocinnamic acid was obtained and no trans stilbene could be isolated.

Weygand[123] has recommended the use of molecular compound formation to separate geometrical isomers. For instance, small amounts of stilbene were removed from isostilbene through formation of a molecular compound of the former isomer with sym-trinitrobenzene. After complete removal of the stilbene the iso-stilbene was obtained in crystalline form. However, formation of molecular compounds by either cis or trans isomers does not occur with sufficient regularity for the method to be of great use.

In all cases reported only one geometrical isomer has been isolated from the Meerwein reaction. All these products are believed to have the trans configuration although definite proof has only been forthcoming in a few cases[59,122]. For instance, coupling of benzene diazonium chloride with cinnamic acid produces stilbene, the trans configuration of which has been clearly demonstrated by various independent methods.

In the present series of compounds the main product from the decarboxylation of the Perkin acids has been assumed to possess the cis configuration and the higher melting, less soluble isomers formed from them by heating with iodine in benzene to be the trans forms. The high melting forms were also obtained in the two Meerwein reactions studied. For the nitro, methoxy, and chloro compounds the supposed trans isomers exhibited liquid crystal formation. In the case of the p-dimethylamino- compound melting was accompanied by widespread decomposition and there was no possibility of observing liquid crystal formation. The property of liquid crystal formation is shown by numbers of trans isomers and has been recommended[57] as a criterion for distinguishing them from the cis compounds.

It has been suggested[119] that the rate at which bromine is removed from the trans and cis stilbene dibromides by iodide ions according to the reaction

$$RCHBr \cdot CHBrR' + 3I^- \longrightarrow RCH=CHR' + I_3^- + 2Br^-$$

can be used as a method for distinguishing between cis and trans isomers. In the cases[119] investigated bromine was eliminated much more rapidly from the dibromides from the trans compounds (i.e., from the meso dibromides). This method has not been investigated in the present work. Other well known physical methods[120] for distinguishing between the cis and trans isomers are dipole moment, X-ray, and ultra violet absorption measurements. In the case of dipole moments, the moments of the individual groups may obscure those due to their cis or trans configuration. Moreover, the apparatus necessary for the measurements is not always available, a difficulty which applies also to X-ray methods, which have the additional disadvantage of requiring more time than most of the other methods.

b). Experimental.

Type B Compounds.

cis-(2-Fluorenyl)-p-nitrocinnamic acid. Fluorene-2-acetic acid (5.6 g.; 1/40 mol.; dried at 110°), p-nitrobenzaldehyde (4 g.; 5% excess), triethylamine (I.C.I. product dried over potassium hydroxide; 2.52 g.; 1/40 mol.) and acetic anhydride (23.2 ml.; 25.5 g.; 1/4 mol.) were heated at 85-95° (oil bath temperature) for 11-11.5 hours. The product, while still warm, was poured into cold water, and after standing 12 hours or longer, the mixture was heated 1-2 hours on the water bath until

the oily solid had completely solidified. It was cooled, collected and washed. The yield of crude acid was nearly quantitative. Purified through its sparingly soluble sodium or potassium salt it yielded 4.5 g. of a product of m.p. 259-261°, which was sufficiently pure for decarboxylation. For analysis the acid was crystallised twice from 90% acetic acid and then from alcohol, when it was obtained as bright yellow platelets of m.p. 262-263° (decomp.). (Found: C, 73.9; H, 4.28; N, 3.94. $C_{22}H_{15}O_4N$ requires C, 73.9; H, 4.23; N, 3.92%).

cis-α-(2-Fluorenyl)-β-(p-nitrophenyl)-ethylene. The copper powder used in this and subsequent decarboxylations was prepared according to the method of Gattermann and stored under water. It was dried on a porous tile immediately before use. In later decarboxylations copper chromite catalyst was often used in place of the copper powder. There was no significant different in yields in any of the examples studied. Cis-α-(2-fluorenyl)-p-nitrocinnamic acid (1.8 g.; 0.005 mol.) was dissolved on warming in quinoline (20 ml.; dried over potassium hydroxide) and 2-3 times its weight of copper powder was added. The mixture was maintained at 210-215° (metal bath temperature) for 10-12 minutes, when the initial brisk reaction had practically ceased. The still warm mixture was poured into benzene,

filtered, and the benzene layer washed repeatedly with dilute hydrochloric acid, then with water and finally with sodium carbonate solution. Acidification of the alkaline extract showed that decarboxylation was practically complete. The benzene solution was dried over sodium sulphate and chromatographed on alumina (B.D.H.). A broad homogeneous yellow band passed first down the column followed by a number of bands which varied from orange to dark red. It was necessary to use several columns to effect complete separation of the yellow material. Removal of the benzene from the yellow eluate left a yellow sticky crystalline residue, which after crystallisation from petroleum ether (80-100°) containing a little benzene gave 150 mgm. of bright yellow needles of m.p. 134-135.5°. Crystallisation from alcohol gave bright yellow needles, m.p. 134-136°. (Found: C, 80.7; H, 4.92; N, 4.54. $C_{21}H_{15}O_2N$ requires C, 80.4; H, 4.83; N, 4.47%). The eluates from the above mentioned orange and red bands were examined. The orange bands yielded a crystalline material, but it could not be obtained pure.

In view of the poor yields obtained with the quinoline and copper powder or copper chromite method of decarboxylation in this case, a number of other methods of decarboxylation were tested, but they either failed to effect decarboxylation or, if effective, brought about wide-spread decomposition of the molecule.

trans-α-(2-Fluorenyl)-β-(p-nitrophenyl)-ethylene (XXXVIII).

(a). cis-α-(2-Fluorenyl)-β-(p-nitrophenyl)-ethylene was dissolved in pure, dry benzene, a few crystals of iodine added and the benzene distilled, when the trans isomer usually separated from the hot solution during the distillation. The crystalline residue was maintained at 140-150° (oil bath temperature) for a further 10-15 minutes, then cooled, stirred with sulphurous acid solution, collected and washed. After crystallisation from benzene/alcohol (4:1) it melted at 222-223° to an opalescent liquid which became clear at 252-253° (slight decomp.). (Found: C, 80.6; H, 4.93; N, 4.39. $C_{21}H_{15}O_2N$ requires C, 80.4; H, 4.83; N, 4.47%).

(b). A mixture of 2-aminofluorene (0.91 g.; 0.005 mol.), concentrated hydrochloric acid (1.5 ml.) and water (7.5 ml.) was heated to 100° and cooled rapidly to 0° with vigorous stirring. This suspension of the hydrochloride was diazotised at 0-2° with sodium nitrite (0.4 g.) in water (2.5 ml.). After standing 1 hour at 0-2°, the suspension of the diazonium salt was added to p-nitrocinnamic acid (0.97 g.; 0.005 mol.) suspended in "analar" acetone (130 ml.) and solutions of sodium acetate (2 g. in 6.5 ml. of water) and cupric chloride (0.86 g. in 2.5 ml. of water) were added immediately. No reaction took place at room temperature (15-20°) and the temperature of the mixture was cautiously raised until steady evolution of gas set in and

the diazonium salt and the p-nitrocinnamic acid steadily disappeared (1.5 hours)(bath temperature 30-40°). The reaction mixture was then steam distilled, when acetone (probably containing some chloroacetone) passed over and then a mixture of neutral solids, subsequently identified as fluorene and 2-chlorofluorene. The brown powdery, non-volatile residue was filtered, then digested with warm sodium carbonate solution and again filtered. Acidification of the combined filtrates gave 0.85 g. of p-nitrocinnamic acid. The dry carbonate insoluble residue was shaken with benzene and the resulting deep brown solution passed through a column of alumina (B.D.H.; 2 x 13 cm.). A dark zone separated at the top of the column while a bright yellow zone passed steadily down the column and was eluted. Removal of the solvent from this yellow eluate left a slightly sticky, yellow crystalline residue which after washing with a little alcohol had m.p. 218.5-219.5° (to an opalescent liquid)(weight 15-20 mgm.). After crystallisation from benzene/alcohol (4:1), the product had m.p. 221.5-222.5° to an opalescent liquid which became clear at 252-253° (slight decomp.). A mixed m.p. with the product obtained by method (a) gave no depression.

(c). Pure 2-fluorenyl-p-nitrobenzyl-ketone (XXXIX) (see below p.110) was mixed with excess of an approximately 1 molar solution of aluminium isopropoxide in dry, thiophene free

benzene and the benzene slowly distilled through a rod and disc fractionating column (20 cm.) until no further test for acetone was obtained in the distillate (about 10 hours). Benzene was added to the reaction mixture at intervals during the distillation to maintain the volume constant. The reaction mixture was decomposed with ice cold hydrochloric acid and the benzene subsequently distilled. The residual suspension of a yellow crystalline solid was filtered and the residue washed. The product had m.p. 172-175°, and after crystallisation from alcohol melted at 175-176.5°. A second crystallisation from alcohol did not alter the melting point. (Found: C, 76.2; H, 5.27; N, 4.25. $C_{21}H_{17}O_3N$ requires C, 76.1; H, 5.17; N, 4.23%).

The carbinol was dehydrated by boiling with acetic anhydride containing dry hydrogen chloride for $3\frac{1}{2}$ hours. After decomposition of the acetic anhydride the product was recovered as a bright yellow solid of m.p. 219-221° (to an opalescent liquid which became clear at 247-248°). After crystallisation from benzene/alcohol (4:1) it melted at 222-223° to an opalescent liquid which cleared at 253.5-254.5°. A mixed melting point with the product from (a) gave no depression.

trans-α-(2-Fluorenyl)-β-(p-acetylaminophenyl)-ethylene.

A mixture of trans-α-(2-fluorenyl)-β-(p-nitrophenyl)-ethylene, stannous chloride and equal volumes of acetic acid and concentrated hydrochloric acid was heated on the water bath until reduction of the nitro group was complete (ca. 4 hours). On cooling the reddish precipitate was collected and worked up by standard procedures, but the amine did not crystallise well and was converted to its acetyl derivative by heating with acetic anhydride. After crystallising from acetic acid the acetyl compound had m.p. 273-275° (decomp.). A second crystallisation from acetic acid gave a pale straw coloured crystalline product, m.p. 278-280° (decomp.).
(Found: C, 85.0; H, 5.82; N, 4.69. $C_{23}H_{19}ON$ requires C, 84.90; H, 5.89; N, 4.31%).

cis-α-(2-Fluorenyl)-p-chlorocinnamic acid. The p-chlorobenzaldehyde was prepared according to the Organic Syntheses directions[61] for the p-bromo compound except that it was found necessary to carry out the hydrolysis of the diacetate and subsequent manipulations as nearly as possible in a nitrogen atmosphere to prevent complete oxidation of the aldehyde. Fluorene-2-acetic acid (8.96 g.; 0.04 mol.; dried at 110°), triethylamine (6 ml.; 0.04 mol., the same quality as in previous Perkin reactions), acetic anhydride (37.2 ml.) and

p-chlorobenzaldehyde (6.8 g.; 20% excess) were mixed and heated under a nitrogen atmosphere at 85-95° for 11.5 hours. The product while still warm was poured into water and after standing 12 hours or longer it was heated on the water bath for 1-2 hours until the oily solid had completely solidified. The crude acid was converted to its sparingly soluble sodium salt and the latter collected and washed with benzene until the washings were colourless. The residual salt was dissolved in hot water (500 ml.; charcoal) and filtered. The cream coloured acid (6.9 g.) recovered by acidification of the filtrate had m.p. 236.5-238.5°. For analysis it was crystallised from benzene giving a product of m.p. 242.5-243.5° and then 3 times from 90% acetic acid, and again from benzene giving cream coloured needles or prisms, m.p. 245.0-245.5°. (Found: C, 76.0; H, 4.35; Cl, 10.33. $C_{22}H_{15}O_2Cl$ requires C, 76.2; H, 4.36; Cl, 10.23%).

cis- α-(2-Fluorenyl)-β-(p-chlorophenyl)-ethylene. A solution of α-(2-fluorenyl)-p-chlorocinnamic acid (1.73 g.; 0.005 mol.) in quinoline (20 ml.) was heated with 2-3 g. of copper powder at 205-210° (metal bath temperature) until the initial brisk reaction had subsided (10-12 minutes). The mixture, while still warm, was poured into petroleum ether (60-80°; 250 ml.), filtered, and the filtrate extracted successively with dilute hydrochloric acid and then sodium carbonate solution as

described for the corresponding nitro compound. No unchanged acid was recovered on acidification of the sodium carbonate extract. The dry petroleum ether extract was chromatographed on alumina (B.D.H.). A broad homogeneous colourless band, weakly fluorescent in ultra violet light, passed first down the column, followed by a narrow colourless more strongly fluorescent band (the trans isomer), and thenby a heterogeneous yellow zone. On removal of the solvent the first colourless eluate left an almost colourless, slightly greasy residue of m.p. 97-99° (0.82 g.; 54% of the theoretical yield). For analysis and biological examination it was crystallised from alcohol, giving colourless needles, m.p. 103.5-104.0°. It was crystallised again from alcohol giving a product of the same m.p. (Found: C, 83.5; H, 5.16; Cl, 11.57. $C_{21}H_{15}Cl$ requires C, 83.3; H, 5.00; Cl, 11.71%).

trans-α-(2-Fluorenyl)-β-(p-chlorophenyl)-ethylene. Pure cis-α-(2-fluorenyl)-β-(p-chlorophenyl)-ethylene was isomerised by heating with iodine in benzene exactly as described for the corresponding nitro compound. The crude product had m.p. 220-222° to an opalescent liquid. It was crystallised from benzene containing 15% alcohol, giving colourless crystals (opalescent plates) of m.p. 225-226° to an opalescent liquid which cleared at 238-239°. After two further crystallisations from the same

solvent mixture it had m.p. 224.5-225° to an opalescent liquid clearing at 239-240°. (Found: C, 83.2; H, 5.00; Cl, 11.49. $C_{21}H_{15}Cl$ requires C, 83.3; H, 5.00; Cl, 11.71%).

cis-α-(2-Fluorenyl)-p-methoxycinnamic acid. (a). A mixture of fluorene-2-acetic acid (2.24 g.; 0.01 mol.), anisaldehyde (1.46 ml.; 20% excess), triethylamine (1.38 ml.; 0.01 mol.) and acetic anhydride (5 ml.) was heated at 90-95° for 11 hours. The product while still warm was poured into water and after standing 12 hours or longer the crude acid was purified through its sparingly soluble sodium salt in an analogous manner to the chloro compound. Yield 1.25 g. (36% of the theoretical amount) of a colourless acid of m.p. 271-272° (slight decomp.). It was crystallised from 90% acetic acid giving a product (pale cream needles or prisms) of m.p. 273-274.5°. Two further crystallisations from alcohol did not alter the m.p. (Found: C, 80.7; H, 5.17; $C_{23}H_{18}O_3$ requires C, 80.7; H, 5.30%). When the above preparation was carried out on twice the scale a 43% yield was obtained.

(b). A mixture of fluorene-2-acetic acid (2.24 g.), anisaldehyde (1.46 ml.), finely powdered, freshly fused potassium acetate (1 g.; 0.98 g. ≡ 0.01 mol.) and acetic anhydride (5 ml.) was heated at 110-120° for 8 hours. By this time the

separation of a little dark resinous matter had commenced and heating was stopped. The product, while still warm, was poured into cold water and after standing 12 hours or longer the crude acid was purified through its sodium salt as under (a). Yield 0.9 g. of a product of m.p. 261-265°.

cis-α-(2-Fluorenyl)-β-(p-methoxyphenyl)-ethylene. α-(2-Fluorenyl)-p-methoxycinnamic acid (1.71 g.; 0.005 mol.) was decarboxylated by heating in quinoline solution (20 ml.) with 2-3 times its weight of copper powder at 205-210° (metal bath temperature) for 10-12 minutes. The product was worked up as described for the corresponding chloro compound. 0.9 G. (60%) of a colourless, slightly greasy crystalline product was obtained after chromatography. For analysis and biological examination it was crystallised from alcohol giving a product of m.p. 92-92.5°. Crystallised again from alcohol the product formed a mass of shiny plates, m.p. 91-91.5°. (Found: C, 88.7; H, 6.22. $C_{22}H_{18}O$ requires C, 88.5; H, 6.08%).

When the decarboxylation was carried out on half the above scale the yield rose to 70% of the theoretical amount. As with the chloro compound, a thin band of the more strongly adsorbed trans isomer passed down the column between the cis isomer and the coloured impurities. The eluates from the

strongly adsorbed yellow bands on the column were examined. They contained crystalline material but it could not be purified.

trans-α-(2-Fluorenyl)-β-(p-methoxyphenyl)-ethylene. cis-α-(2-Fluorenyl)-β-(p-methoxyphenyl)-ethylene was isomerised by exactly the same method as used for the nitro and chloro compounds. After crystallisation from benzene containing 10% of alcohol the product had m.p. 225-226° to an opalescent liquid which cleared at 265-266° (slight decomp.). A second crystallisation gave a product (colourless plates with a pearly sheen) of m.p. 226-227° to an opalescent liquid becoming clear at 264-265° (slight decomp.). (Found: C, 88.6; H, 6.00. $C_{22}H_{18}O$ requires C, 88.5; H, 6.08%).

cis-α-(2-Fluorenyl)-cinnamic acid. A mixture of fluorene-2-acetic acid (2.24 g.; 0.01 mol.), benzaldehyde (1.22 ml.; 20% excess), triethylamine (1.38 ml.; 0.01 mol.) and acetic anhydride (5 ml.) was heated at 90-100° for 11-11.5 hours. The product was worked up as in the cases of the chloro and methoxy compounds and gave 1.89 g. (60.5% of the theoretical amount) of an acid of m.p. 217-219° after purification through the sodium salt. For analysis the acid was crystallised three times from 90% alcohol giving a mass of small, colourless needles, m.p. 220-222° (slight decomp.). (Found: C, 84.4;

H, 5.24. $C_{22}H_{16}O_2$ requires C, 84.6; H, 5.17%).

cis-α-(2-Fluorenyl)-β-phenyl-ethylene. cis-α-(2-Fluorenyl)-cinnamic acid was decarboxylated by heating its quinoline solution with copper powder as described for the chloro and methoxy analogues. It was purified according to the procedure described for these compounds. The cis isomer passed down the alumina column as a weakly fluorescent, colourless zone. It was followed by a narrow, more strongly fluorescent colourless zone which on elution and removal of the solvent left a small quantity of the trans isomer. As in previous cases more strongly adsorbed coloured zones followed the trans isomer but the materials from them could not be purified. The yield of the cis compound recovered from the chromatography varied from 74-64% of the theoretical amount starting with 0.5-1.5 g. of acid. For analysis and biological examination the colourless, slightly greasy material from the chromatography was crystallised twice from alcohol giving shiny plates of m.p. 74.5-75.0°. (Found: C, 94.2; H, 5.98. $C_{21}H_{16}$ requires C, 94.0; H, 6.00%).

trans-α-(2-Fluorenyl)-β-(phenyl)-ethylene (XXXVII).

(a) The pure cis isomer was isomerised by exactly the same method as described for the nitro, chloro and methoxy compounds. The crude product crystallised from alcohol, in which it was

sparingly soluble, in tiny plates of silky appearance, m.p. 218-219°.

(b) A mixture of 2-aminofluorene (2.6 g., 1/70 mol.), concentrated hydrochloric acid (4 ml.) and water (20 ml.) was heated to 100° and then cooled rapidly with vigorous stirring to 0-2°. The suspension of the hydrochloride was diazotised with sodium nitrite (1.1 g.; 0.98 g. = 1/70 mol.) in water (5 ml.). The separation of the sparingly soluble, yellow diazonium salt soon commenced and the mixture was let stand at 0-2° for 1 hour to complete the reaction. The suspension of the diazonium salt was poured into a solution of cinnamic acid (2.1 g.; 1/70 mol.) in "analar" acetone (30 ml.), and sodium acetate (4.7 g.; 1/30 mol.) in water (15 ml.) and then cupric chloride (1 g.) in water (3 ml.) were added immediately. The temperature of the mixture was 14° and there was no noticeable rise in temperature. The mixture was allowed to stand at room temperature (16°) with frequent shaking until the yellow diazonium salt had completely disappeared and the slow evolution of gas had ceased (about 24 hours). The mixture was diluted with water and steam distilled, when acetone (probably containing some chloroacetone) passed over followed by some fluorene. The residue in the flask was filtered, then digested with warm sodium carbonate solution and again filtered. Acidification of these filtrates gave

0.6 g. of cinnamic acid of m.p. 131-133°. The carbonate insoluble residue was insoluble in sodium hydroxide solution. After drying it was dissolved in benzene and the solution passed through a column of alumina (B.D.H.), when a yellow zone passed rapidly down the column followed by a dark heterogeneous zone. The benzene was removed from the yellow eluate and the yellow crystalline residue dissolved in petroleum ether (60-80°). On passing this solution through a second column of alumina the yellow impurity was strongly adsorbed and a colourless crystalline residue of m.p. 214-216° was recovered from the eluate. After 2 crystallisations from alcohol it gave tiny silky-looking plates of m.p. 218.5-219.5°. (Found: C, 94.0; H, 6.05. $C_{21}H_{16}$ requires C, 94.0; H, 6.00%). A mixed m.p. with the product obtained under (a) gave no depression.

trans-α-(2-Fluorenyl)-β-(p-dimethylaminophenyl)-ethylene (XLIV). A mixture of dry, powdered fluorene-2-acetic acid (3.36 g.; 0.015 mol.), p-dimethylaminobenzaldehyde (2.4 g.; B.D.H. Analar.) and piperidine (1.5 ml.) was heated to 130-140° (oil bath temperature), when a reaction set in and the mass liquefied. After 8½ hours at 130-140° the reddish brown viscous product was digested with warm sodium carbonate solution and the resulting yellow suspension extracted repeatedly with chloroform in which the bulk of the alkali in-

soluble material dissolved. The combined chloroform extracts were washed once with water and the chloroform removed, leaving a dark tarry residue which was digested with 50 ml. of hot alcohol and allowed to cool. The yellow solid which separated was collected and washed well with alcohol. Yield 0.85 g.; m.p. 253-255° (decomp.). After crystallising from benzene/alcohol (4:1) the product had m.p. 259-261° (decomp.). After crystallising twice more from the same solvent mixture XLIV was obtained as a pale yellow shiny crystalline mass, m.p. 259-261° (decomp.). (Found: C, 88.8; H, 6.87; N, 4.55. $C_{23}H_{21}N$ requires C, 88.7; H, 6.80; N, 4.50%). The alkaline layer after extraction with chloroform (see above) was heated to coagulate a little tarry material, cooled and filtered (filter aid). Acidification with acetic acid gave 0.9 g. of a crude acidic product which after crystallising twice from 50% acetic acid (charcoal) was shown to be fluorene-2-acetic acid by m.p. and mixed m.p.

<u>cis-α-(2-Fluorenyl)-p-aminocinnamic acid</u>. cis-α-(2-Fluorenyl)-p-nitrocinnamic acid was reduced with ferrous sulphate and ammonia exactly as described for the ortho isomer (p.68) except that a coarse grade filter aid was now available and greatly facilitated filtration and washing of the iron hydroxide precipitate. Acidification of the alkaline filtrates with acetic acid gave the crude amino acid. I t was collected,

dissolved in hot sodium carbonate solution and the solution filtered (filter aid). The acid recovered by acidification of the filtrate with acetic acid had m.p. 247-249° (decomp.) and weighed 2.2 g. (from 2.7 g. of the nitro acid). After several crystallisations from 90% alcohol the acid crystallised in dull yellow crystals, m.p. 250.5-252° (decomp.).

(Found: C, 80.9; H, 5.40; N, 4.23. $C_{22}H_{17}O_2N$ requires C, 80.7; H, 5.25; N, 4.28%).

Type C Compounds.

α-(2-Fluorenyl)-p-amino-dihydrocinnamic acid (XL). Attempts to reduce the ethylenic bond and the nitro group of α-(2-fluorenyl)-p-nitrocinnamic acid by shaking its alcoholic or acetic acid solutions with hydrogen (atmospheric pressure) and palladium black[24] did not yield a satisfactory product. When an alcoholic suspension of the nitro acid was shaken with Raney nickel and hydrogen (20-25 atmospheres) at 40-60° satisfactory reduction was obtained. After filtration of the catalyst removal of the alcohol left a slightly discoloured crystalline residue. After preliminary purification through its sparingly soluble sodium salt the acid was crystallised from alcohol giving cream coloured crystals, m.p. 250-251.5° (decomp.). (Found: C, 80.3; H, 5.88; N, 4.29.

$C_{22}H_{19}O_2N$ requires C, 80.2; H, 5.81; N, 4.25%). Preliminary attempts to convert the COOH group to NH_2 using the Schmidt reaction have been inconclusive.

2-Fluorenylmethyl-p-methoxyphenylketone (XLI). Fluorene-2-acetic acid (2.24 g.; 0.01 mol.) was converted to its acid chloride by heating with thionyl chloride, the excess of the latter being removed under reduced pressure. The acid chloride dissolved in carbon disulphide (analar; 30 ml.) was mixed with anisole (1.25 ml.) and cooled in an ice bath. Finely powdered aluminium chloride (1.5 g.) was added, when a brisk reaction took place which had subsided in 1-2 hours. After standing 5 hours in the ice bath and overnight at room temperature the product was decomposed with ice and hydrochlorid acid in the usual way. The unchanged anisole was removed in steam, and after cooling the insoluble residue collected, washed with dilute hydrochloric acid and then with water. Vacuum sublimation gave 1.6 g. (51% of the theoretical amount) of a product of m.p. 172-177°. This was crystallised from 90% acetic acid, giving a mass of colourless needles, m.p. 183-184°. When subsequently crystallised from acetone the m.p. was not raised. (Found: C, 84.4; H, 5.92. $C_{22}H_{18}O_2$ requires C, 84.0; H, 5.77%).

2-Fluorenylmethyl-p-methoxyphenyl-ketoxime. A mixture of 2-fluorenylmethyl-p-methoxyphenyl-ketone (0.74 g.; 0.0024 mol.), hydroxylamine hydrochloride (0.35 g.), hydrated sodium acetate (0.68 g.), alcohol (75 ml.) and water (3 ml.) was refluxed. The ketone dissolved in 1-2 hours, and after refluxing 4½ hours the mixture was filtered hot to remove precipitated sodium chloride. On cooling, the colourless oxime separated from the filtrate, m.p. 193-196° (yield, 0.62 g.). A further quantity of less pure material was recovered from the filtrate. For analysis the product was crystallised twice from alcohol, giving colourless crystals of m.p. 197.5-199° (slight decomp.). (Found: C, 80.3; H, 5.92; N, 4.37. $C_{22}H_{19}O_2N$ requires C, 80.2; H, 5.81; N, 4.25%).

Reduction of the oxime with sodium amalgam/acetic acid. Following the directions of Dodds, Lawson and Williams[62] for the reduction of compounds of the type $Ar.CH_2.C = NOH.Ar'$, the above oxime was suspended in a mixture of alcohol and acetic acid at 50-60° and treated with 2.5% sodium amalgam, sufficient acetic acid being added to maintain the solution acid. It was not found possible to purify the colourless product (no unchanged oxime was recovered) and in an attempt to prepare the acetyl derivative of the supposed amine (XLII), the product was refluxed for 10 minutes with acetic anhydride

containing a few drops of concentrated sulphuric acid. The still warm solution was poured into water, and after decomposition of the anhydride the product was collected and washed. It was crystallised 5 times from benzene containing 10% alcohol giving a mass of small silky looking plates of m.p. 226-227.5° to an opalescent liquid which cleared at 262-262.5° (slight decomp.). (Found: C, 88.5; H, 5.88. $C_{22}H_{18}O$ requires C, 88.5; H, 6.08%). A mixed m.p. with trans-α-(2-fluorenyl)-β-(p-methoxyphenyl)-ethylene of the same m.p. gave no depression. Presumably during the reduction or attempted acetylation ammonia split off from the amine (XLII) leaving the ethylenic derivative.

Reduction of α-(2-fluorenyl)-β-(p-methoxyphenyl)-ethylene.

Pure cis-α-(2-fluorenyl)-β-(p-methoxyphenyl)-ethylene (0.298 g.; 0.001 mol.) in acetic acid (50 ml.) was shaken with hydrogen (1 atmosphere) and palladium charcoal[23] at room temperature until hydrogen in about 10% excess of the theoretical amount had been absorbed (10 minutes), when absorption ceased. After removal of the catalyst the filtrate was diluted with water, when a colourless precipitate (XLIII) separated. It had m.p. 154-155° and after crystallisation from alcohol gave colourless prisms of the same m.p. (Found: C, 87.8; H, 6.74. $C_{22}H_{20}O$ requires C, 88.0; H, 6.72%).

(2-Fluorenyl)-p-nitrobenzyl-ketone (XXXIX). Dry, powdered p-nitrophenylacetic acid (18.1 g.; 0.1 mol.) was added with shaking, portionwise, over 10-15 minutes, to a mixture of phosphorus pentachloride (23 g., 10% excess) and dry, thiophene free benzene (30 ml.). After the initial reaction had subsided, the mixture was heated at 80-85° (oil bath temperature) for 20 minutes and the benzene/phosphorus oxychloride then removed under reduced pressure at temperatures $\not>$ 85°. Fluorene (16.6 g.; 0.1 mol.) and carbon disulphide (analar; dried over calcium chloride; 45 ml.) were then added, and when the mixture had come to room temperature, finely powdered aluminium chloride (19 g.) was added gradually (30-40 minutes). A brisk reaction proceeded and the mixture became slightly warm. After standing at room temperature for 4 hours the mixture had set to a solid mass. It was decomposed with ice and hydrochloric acid in the usual way and then steam distilled until the bulk of the unchanged fluorene was removed. While still hot the non-volatile residue was filtered and washed, and then digested with warm sodium carbonate solution and again filtered. From the two filtrates about 2 g. of p-nitrophenylacetic acid were recovered. The crude brown residue (26.2 g.) underwent much decomposition when sublimed at 0.1 mm., and a preliminary purification was effected by passing its benzene solution through a column of silica. Removal of the solvent and

washing the residue with benzene left a yellow crystalline material (about 50% recovery), which after crystallisation from benzene had m.p. 206.5-208.5°. Crystallised from acetic acid it had m.p. 208.5-210.5° (pale yellow prisms). A final crystallisation from benzene gave cream coloured thin plates of m.p. 210.5-211.5°. (Found: C, 76.8; H, 4.73; N, 4.30. $C_{21}H_{15}O_3N$ requires C, 76.6; H, 4.59; N, 4.26%).

The reduction of 2-fluorenyl-p-nitrobenzyl-ketone. In addition to the aluminium isopropoxide reduction of this ketone (p.94) other methods of reduction were investigated.

a). Hydrogenation of an alcoholic solution of XXXIX in the presence of Pd/charcoal catalyst and a little hydrochloric acid gave a high melting product which could not be purified.

b). A mixture of the nitro ketone, acetic acid/concentrated hydrochloric acid (2:1), and stannous chloride was heated on the water bath until reduction of the nitro group was complete (a purple colour is no longer obtained with alcoholic sodium hydroxide; cf. 130) (7-9 hours). After diluting the mixture with concentrated hydrochloric acid and cooling the precipitate was collected and stirred with concentrated sodium hydroxide solution and again filtered and washed. The crude amine was not readily purified and was boiled for a short time with excess acetic anhydride. After decomposition of the excess

acetic anhydride the dark coloured product was crystallised from petroleum ether (80-100°)/benzene (3:1) (charcoal), when it was obtained as a nearly colourless mass of plates. Repeated crystallisations from the same solvent mixture gave colourless, shiny plates, m.p. 201-202.5°. (Found: C, 78.69; H, 5.50; N, 4.02. $C_{25}H_{21}O_3N$ requires C, 78.31; H, 5.52; N, 3.65%. $C_{23}H_{19}O_2N$ requires C, 80.91; H, 5.61; N, 4.10%). The analysis indicates a diacetyl derivative (XLV) contaminated with a little of the mono-acetyl compound.

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Appendix.

The biological examination of certain of the Fluorene Derivatives.

Professor A. Haddow, Chester Beatty Research Institute, the Royal Cancer Hospital, has undertaken to examine the following compounds for tumour inhibitory and/or carcinogenic activity. The compounds are (2':1'-naphtha)-2:3-fluorene (II), (1':2'-naphtha)-1:2-fluorene (XXVII), the cis and trans isomers of α-(2-fluorenyl)-β-(p-methoxy-phenyl)-ethylene, α-(2-fluorenyl)-β-(p-chloro-phenyl)-ethylene, α-(2-fluorenyl)-β-(phenyl)-ethylene and the trans isomer of α-(2-fluorenyl)-β-(p-dimethyl-aminophenyl)-ethylene. The examination is not yet complete but Professor Haddow has kindly supplied the following preliminary report, including a brief account of the experimental methods employed.

The tests for inhibitory activity have been carried out using the Walker carcinoma 256 growing in an inbred strain of albino rat. On the day following subcutaneous tumour implantation, the test series is injected intraperitoneally with 2 cc. of a sterile solution, or, if necessary, a sterile fine suspension, of the compound being examined. The dose has been approximately 250 mg. per kg. body weight. The growth of the tumours is inspected daily and compared with that in a control series implanted from the same tumour at the same time and

treated by intraperitoneal injection of the solvent alone, in this case peanut oil. The final result is determined by a comparison of weights of tumours, after their removal between two and three weeks from the start of the experiment.

So far only (1':2'-naphtha)-1:2-fluorene has given clear evidence of inhibitory properties. It is also being tested for carcinogenicity. In this case application was to the skin of mice, using an 0.1% solution of the substance in benzene. Papillomata have now appeared on some of the mice so treated. (2':1'-Naphtha)-2:3-fluorene is also being tested for carcinogenicity.