Part I. Synthesis of tumour-inhibiting compounds.

Part II. Syntheses of 1:9-phenylenecarbazole.

T H E S I S

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PART I.

Synthesis of tumour-inhibiting compounds.

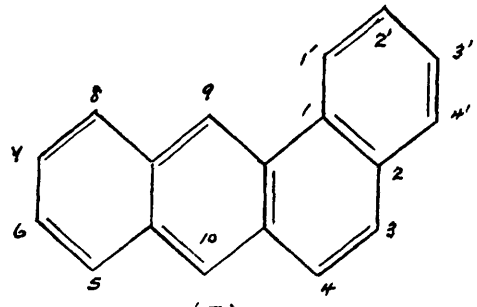
C O N T E N T S.

Part I.

INTRODUCTION.

The discovery that cancer can be produced in animals by the action of polycyclic hydrocarbons and their derivatives, either by application to the skin or by intravenous injection, was a direct result of the observation that cancer is to some extent an occupational disease, especially prevalent among workers in the coal tar industries. The inference that 'tar cancer' arises as a result of prolonged contact with a chemical compound present in coal tar was confirmed in 1915 when Yamagiwa and Ichikawa[1] succeeded in producing tumours by the continued application of a coal tar distillate to the ear skin of rabbits. Bloch and Dreiffus[2] showed that the cancer-producing substance is present in the high-boiling, neutral, nitrogen-free fractions, and is capable of forming a stable complex with picric acid. The possibility of this substance being a polycyclic aromatic hydrocarbon was strengthened a few years later when Kennaway[3] found that the complex mixture of hydrocarbons produced by Schroeter[4] by the action of aluminium chloride on tetrahydronaphthalene possesses carcinogenic activity. Kennaway also observed that similar activity was shown by the tars obtained by strongly heating mixtures of acetylene or isoprene with hydrogen.

The discovery by Mayneord, in 1927, that all carcinogenic tars have identical fluorescence spectra, with bands at 4000, 4180 and 4400 A.U. led Hieger[5] to examine the fluorescence of a number of hydrocarbons in the hope of identifying the spectrum. Special attention was paid to derivatives of anthracene, the molecular structure of which is known to be responsible for a most intense fluorescence. It was found that 1:2-benzanthracene (I) gives a similar

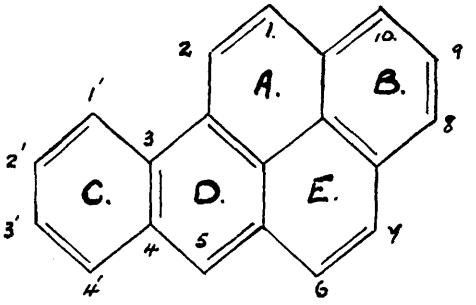


(I)

spectrum in which the three bands are in almost identical positions relative to one another but displaced as a whole away from the visible region. Biological testing showed that 1:2-benzanthracene possesses little if any carcinogenic activity[6] and this led Cook[7] to synthesise a large number of homologues of 1:2-benzanthracene, including all twelve monomethyl derivatives, with the object of obtaining a pure compound having the same spectrum as the cancer-producing tars. Although none of these compounds is the active constituent of tars, a number of them and especially those having substituents in the 5-, 6-, 9- or 10-positions of the 1:2-benzanthracene molecule, are able to produce

tumours in mice.

Working on the assumption that the carcinogenic agent present in coal tar is also responsible for the characteristic fluorescence spectrum, and using fluorescence spectroscopy as a guide in the selection of fractions for further treatment, Cook, Hewett and Heiger[8] embarked on the laborious task of separating the active material from two tons of pitch. After a lengthy process of distillation, solvent extraction, and fractional crystallisation these workers succeeded in isolating a very small quantity of a hydrocarbon which they showed by synthesis to be 3:4-benzpyrene (II)*.



(II)

When applied to the skin of mice in a 3% solution in benzene 3:4-benzpyrene produced tumours in about 100 days[9] and is sufficiently potent to account for the carcinogenic activity of coal tar. Although the possibility of other cancer-producing hydrocarbons being present in tar is not excluded, prolonged contact with small quantities

*Originally termed 1:2-benzpyrene but renamed 3:4-benzpyrene in 1937.

of 3:4-benzpyrene is doubtless responsible for the numerous cases of skin cancer among workers in the coal tar industries.

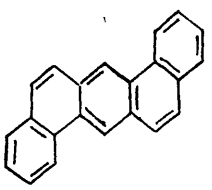
It is noteworthy that while it also contains the ring systems of pyrene (ABDE) and of chrysene (CDAB), 3:4-benzpyrene may be regarded as a derivative of 1:2-benzanthracene (CDEB) substituted at position 10, a position of substitution which has since been observed to be favourable for carcinogenic activity (cf. 10-methyl-1:2-benzanthracene which is actively carcinogenic).

Shortly after the similarity between the fluorescence spectrum of 1:2-benzanthracene and that of the carcinogenic tars had been discovered, Clar[9] published a very simple synthesis of 1:2:5:6-dibenzanthracene (III), a compound first prepared by a more laborious route by Weitzenböck and Klingler[10]. The fluorescence spectrum of this hydrocarbon was found[5] to be of the characteristic three banded type and situated about midway between those of 1:2-benzanthracene and aluminium chloride-treated tetralin.

When 1:2:5:6-dibenzanthracene was applied to the skin of mice in a 3% solution in benzene tumours appeared in about 200 days in a large percentage of the animals treated[6]. This was the first case of the production of

cancer by a pure polycyclic hydrocarbon of known structure. It is noteworthy that while the introduction of suitable substituents into suitable positions of the 1:2-benzanthracene molecule leads to enhanced carcinogenic activity, similar derivatives of 1:2:5:6-dibenzanthracene are for the most part inactive or very weakly active.

Of the other four possible dibenzanthracenes carcinogenic activity has been shown only with the 1:2:7:8-compound (IV)*, synthesised by Cook in 1932[11], and which gave lepithelioma and 3 papillomas in 20 mice[12].



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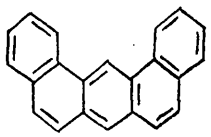

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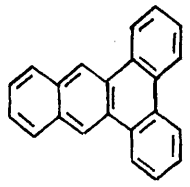

(V)

1:2:3:4-dibenzanthracene (V) was first reported as having feeble activity[6], but the material used was not quite pure, and in a further test with pure hydrocarbon no positive results were obtained[12].

A number of compounds having a superficial molecular resemblance to 1:2:5:6-dibenzanthracene or to 1:2:7:8-dibenzanthracene have been prepared and it is interesting

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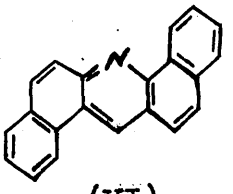
*The compound prepared by Clar (Ber., 1929, 62, 350) and by Fieser and Dietz (Ber., 1929, 62, 1827) and described as 1:2:7:8-dibenzanthracene was shown by Cook (J., 1931, 487) to be 1:2:5:6-dibenzanthracene, the formation of which was due to a molecular rearrangement.

that several of them possess carcinogenic activity. 1:2:5:6-Dibenzacridine (VI) is analogous to 1:2:5:6-dibenzanthracene, and both 1:2:7:8- and 3:4:5:6-dibenzacridine, (VII) and (VIII) respectively, are analogous to 1:2:7:8-dibenzanthracene. Of these dibenzacridines the 1:2:5:6- and 3:4:5:6-compounds have been shown to be carcinogenic[12], although the latent period before the appearance of tumours is much greater (about 350 days)



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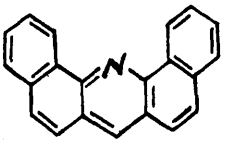

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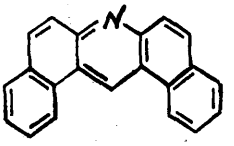

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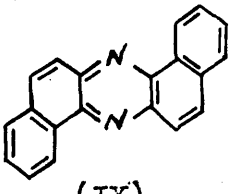


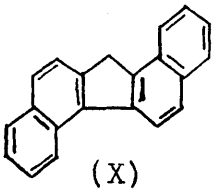
(IX)

than is the case with 1:2:5:6-dibenzanthracene. No result of the biological testing of 1:2:7:8-dibenzacridine has yet been published.

1:2:5:6-Dibenzphenazine (IX), in which both meso-CH-groups of the 1:2:5:6-dibenzanthracene molecule are

replaced by nitrogen atoms, gave negative results when applied to the skin of mice[12], but produced a sarcoma in one of the rats into which it was injected subcutaneously[13].

Tumours of the skin have been produced by application of 1:2:5:6-dibenzfluorene[14] (X) and 1:2:7:8-dibenzfluorene[15] (XI)*, in which the central rings of



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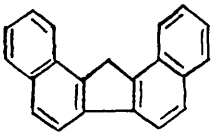

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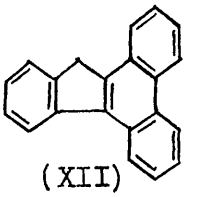
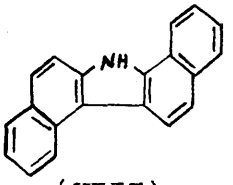


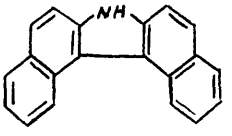
(XII)

1:2:5:6- and 1:2:7:8-dibenzanthracene are respectively contracted to five-membered rings, and 1:2:3:4-dibenzfluorene (XII) acts in the same way[15]. None of these fluorene derivatives gives positive results by subcutaneous injection.

Carcinogenic activity is retained when the central ring of the dibenzanthracene structure is modified both by contraction to a five-membered ring and by replacement of a meso-CH-group by a nitrogen atom. Tumours of the skin of mice were obtained by the action of 1:2:5:6- (XIII)



(XIII)



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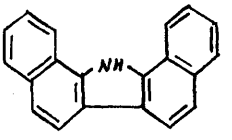

(XV)

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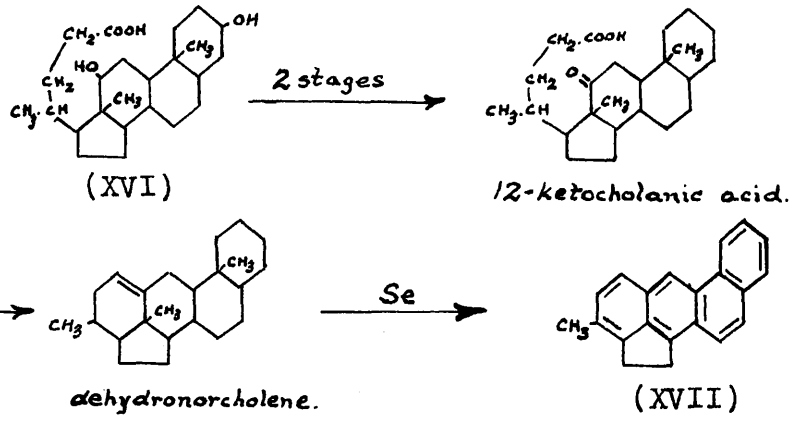
*This compound is the hydrocarbon obtained by Tschitschibabin and Magidson (J.pr.Chem., 1914, 90, 168) by dehydration of di-α-naphthylcarbinol. The structure has subsequently been confirmed by Martin (J., 1941, 679).

and 3:4:5:6-dibenzcarbazole (XIV) and to a slight extent by 1:2:7:8-dibenzcarbazole (XV). The carcinogenicity of the dibenzcarbazoles is important since Boyland and Brues have pointed out[16] that they are possible impurities in the preparation of naphthylamines and may be responsible for the cancer of the bladder prevalent among operatives in the dyestuffs industry.

The production of cancer by polycyclic hydrocarbons assumed an entirely new importance on the recognition that the powerful carcinogen, methylcholanthrene (XVII), is a derivative of 1:2-benzanthracene having substituents in the 5-, 6- and 10-positions. This hydrocarbon was obtained for the first time not by synthesis



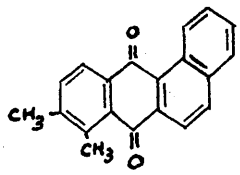
(XVI) 12-ketocholanic acid.

dehydronorcholene. (XVII)

but from the bile acid, deoxycholic acid (XVI), by the above series of changes. In later work methylcholanthrene was also obtained from cholic acid[17], a more abundant constituent of the bile. The degradation of deoxycholic

acid had been carried to within one step of completion by Wieland and Schlichting as early as 1925[18] and was completed independently by Wieland and Dane[19] and by Cook and Haslewood[20]. The structure of methylcholanthrene was proved by its degradation by Cook and Haslewood[20] to 5:6-dimethyl-1:2-benzanthraquinone (XVIII), identical with a specimen prepared synthetically by a method which established its constitution. The structure was further confirmed by the synthesis of methylcholanthrene by Fieser and Seligman[21].

The laboratory preparation of the carcinogenic hydrocarbon from either deoxycholic acid or cholic acid involves reactions all of which are known to occur in the



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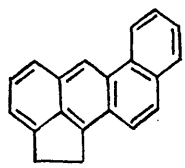


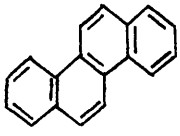
(XIX)

organism: oxidation, hydrogenation, cyclization and dehydrogenation. While this in no way proves that these acids are converted in the body to methylcholanthrene, it appears probable that the etiology of 'spontaneous' cancer may be the metabolic production of methylcholanthrene or related substances from the bile acids, or from the sterols or sex hormones.

The methyl group of methylcholanthrene appears to

be of little significance in determining its carcinogenicity for the parent hydrocarbon, cholanthrene (XIX), synthesised by Cook and others[22] and by Fieser and Seligman[23], is only slightly less potent both in its rate of producing tumours and in the percentage of animals affected[14].

While all the carcinogenic compounds mentioned above are either derivatives of, or superficially related to, 1:2-benzanthracene, it by no means follows that this structure is essential for cancer-producing activity. Thus pure chrysene (XX) produced an epithelioma after a period of 711 days in one mouse out of twenty treated[14], five of which lived for more than 440 days, and 3:4-benzphenanthrene (XXI)*, a hydrocarbon first synthesised by Cook in 1931[24], has been shown to be consistently if



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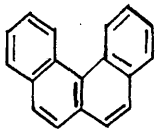
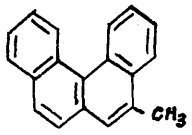


(XXI)



(XXII)

somewhat feebly carcinogenic[12]. A number of homologues of 3:4-benzphenanthrene have since been synthesised, chiefly

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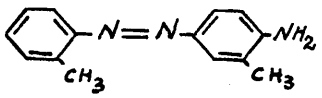
*The hydrocarbon prepared by Weitzenbock and Lieb (Monatsh., 1912, 33, 564) and by Mayer and Oppenheimer (Ber., 1918, 51, 510) and described as 3:4-benzphenanthrene was shown by Cook (J., 1931, 2524) to be 1:2-benzanthracene.

by Hewett. Many of these possess carcinogenic activity and the potency of 2-methyl-3:4-benzphenanthrene (XXII) approaches that of cholanthrene and 3:4-benzpyrene.

Nor is the power to produce cancer confined to polycyclic compounds. As the result of a large volume of outstanding work, carried out almost exclusively by Japanese workers, numerous azo compounds, such as o-amino-azotoluene (XXIII) and p-dimethylaminoazobenzene, 'butter



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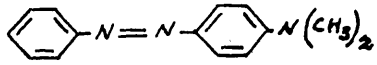
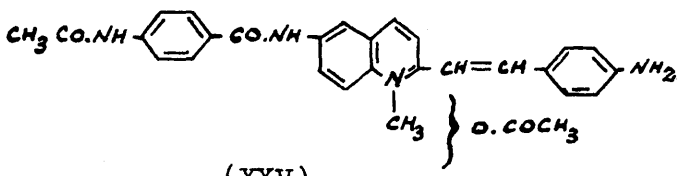


(XXIV)

yellow' (XXIV), have been shown to produce tumours of the liver and of the urinary bladder on application to rats and mice. The experimental production of cancer of the bladder by these compounds is of special interest in view of the prevalence of this type of cancer among workers in the dyestuffs industries. Cancer of the skin has not been produced by means of azo compounds.

One cancer-producing substance quite unrelated in molecular structure to any of the carcinogenic agents discussed above is the trypanocidal 2-(p-aminostyryl)-6-(p-acetylaminobenzoylamino)-quinoline methoacetate (XXV),



(XXV)

synthesised by Browning and his collaborators[25] and found to produce sarcomas in mice at the site of subcutaneous injection.

In view of the fact that cancer, whether spontaneous or produced by the application of a chemical compound, is obviously a condition of most prolific cell-growth, it seems almost paradoxical that Haddow and his collaborators[26] have been able to show that carcinogenic substances have a prolonged inhibitory action on the rate of tumour growth and of body growth in general.

In the experiments on the inhibition of tumour growth intraperitoneal injections of the compound were given at the time of implantation of the tumours. Under these conditions carcinogenic substances, such as 1:2:5:6-dibenzanthracene, 3:4-benzpyrene, methylcholanthrene and 10-methyl-1:2-benzanthracene, caused the grafts to grow much less rapidly than the implants made in uninjected control animals, and in a few cases actually caused partial regression of the tumours. Numerous non-carcinogenic compounds (anthracene, phenanthrene, 1:9-benzanthrone, perylene, fluoranthene, etc.) gave no inhibition of tumour growth under the same conditions. Out of a total of 171 definitely carcinogenic compounds tested, Haddow found that 86.5% showed inhibitory power, while 79.7% of the 79

non-carcinogenic substances employed gave no trace of inhibition. In this startling correlation between cancer-producing and growth-inhibitory properties Haddow finds confirmation of his view that the origin of cancer is the irreversible change of the normal cell, due to the restriction imposed on normal growth by the carcinogenic agent, into a type which can proliferate even in a strongly growth inhibitory medium.

Inhibition of tumour growth was also shown, however, and sometimes to a considerable extent by some apparently non-carcinogenic compounds (e.g., 4'-hydroxy- and 4'-methoxy-3:4-benzpyrene, and 2':3'-naphtha-3:4-pyrene) whereas, on the other hand, such tumour-producing substances as 5-ethyl-1:2-benzanthracene, 9:10-dibenzyl-1:2:5:6-dibenzanthracene, and 3:4-benzphenanthrene, were found to possess no inhibitory properties. These apparent anomalies are explained by Haddow as being possibly due to (a) experimental error, (b) individual variability in the test object, or (c) the fact that for the most part tests for carcinogenic activity have been carried out on mice, whereas the assessment of inhibitory power has been derived almost exclusively from experiments on rats.

During the experiments on the inhibition of tumour growth it was observed that the growth of the rats themselves was retarded although not to the same extent as in

the case of the tumours. Haddow and his collaborators concluded that the inhibitory effect was not specific for tumour growth and that the latter simply shared in a retardation of body growth. This impression was confirmed by the observation that intraperitoneal injection into young rats of such carcinogenic compounds as 1:2:5:6-dibenzanthracene, 1:2:5:6-dibenzacridine and 3:4-benzpyrene causes inhibition of the body growth whereas no effect was shown under the same conditions by the non-carcinogenic hydrocarbons pyrene, fluoranthene, and dodecahydro-1:2-benzanthracene.

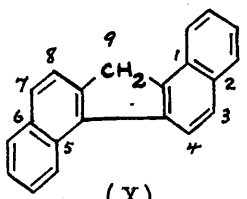
There can be little doubt that some etiological connection exists between growth-inhibitory and cancer-producing activity, but this relationship is qualitative rather than quantitative since some of the more potent carcinogenic compounds have only feeble growth-inhibitory action and vice versa. Thus in order of inhibitory activity 1:2:5:6-dibenzfluorene > 1:2:5:6-dibenzacridine > 1:2:5:6-dibenzanthracene > 3:4-benzpyrene although the order of carcinogenicity is the reverse. Haddow has suggested several probable explanations of this finding but he seems to prefer the possibility that carcinogenicity is dependent on a 'certain optimal, and not a maximal, inhibiting power.'

The possibility that the growth inhibitory activity of carcinogenic compounds may be due to toxic action has been rejected since such toxic agents as colchicine and lead nitrate reduce the rate of growth only so long as the administration is continued. With the carcinogenic substances, on the other hand, the inhibitory effect is prolonged, if not permanent, and is maintained even after the fluorescence spectrum of the compound can no longer be detected.

The discovery of the growth inhibitory powers of the carcinogenic chemical compounds is undoubtedly one of the most promising in the wide field of cancer research, for it may well pave the way to a better understanding of the origin of the disease and help to lay the foundation for a successful chemotherapeutic treatment of cancer.

THEORETICAL.

In view of the marked tumour-inhibitory power of the feebly carcinogenic 1:2:5:6-dibenzfluorene (X) (it produced only 3 epitheliomas and 1 papilloma on application to the skin of 20 mice), it was considered desirable that a variety of the substitution products of the hydrocarbon should be available for examination. The purpose

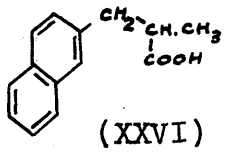


(X)

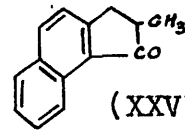
of this work was to prepare these derivatives of 1:2:5:6-dibenzfluorene both by direct substitution and by synthesis.

1:2:5:6-Dibenzfluorene was first synthesised by Cook and his collaborators in 1935[27] during a systematic investigation of the molecular factors necessary for carcinogenic activity. 2-Bromonaphthalene was condensed with the sodium salt of diethyl methylmalonate and the dibasic acid obtained by saponification of the product was readily decarboxylated at 170° to β-2-naphthyl-α-methylpropionic acid (XXVI). This acid, on treatment with anhydrous stannic chloride, ring-closed to 2-methyl-6:7-benzhydrindone (XXVII) from which 3-β-phenylethyl-2-methyl-4:5-benzindene (XXVIII) was obtained by interaction

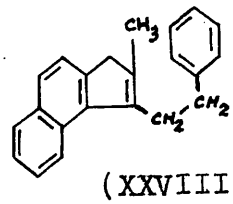
with β-phenylethylmagnesium chloride and dehydration of



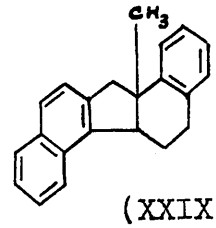
(XXVI)



(XXVII)



(XXVIII)

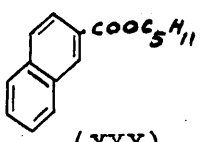


(XXIX)

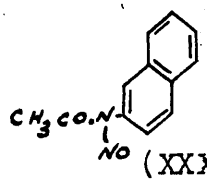
the intermediate carbinol with potassium hydrogen sulphate. The indene (XXVIII) was cyclised by anhydrous aluminium chloride to methyltetrahydrodibenzfluorene (XXIX) which was dehydrogenated by selenium to 1:2:5:6-dibenzfluorene (X).

A simpler synthesis of the dibenzfluorene from more accessible starting materials was carried out by Swain and Todd[28] who utilised a reaction originally discovered by Bamberger[29] and extended by Hey and his collaborators[30] to the synthesis of terphenyl derivatives and of phenylnaphthalenes. N-Nitrosoaceto-2-naphthalide (XXXI) was added in small quantities to a large excess of amyl 2-naphthoate (XXX); the amyl ester, which is liquid at room temperature, was chosen since the reactive nature of the nitroso-compound necessitates the second component of the reaction being in the liquid state. Nitrogen was evolved and from the deep-red solution obtained amyl

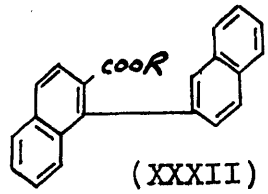
1:2'-dinaphthyl-2-carboxylate (XXXII; $R=C_5H_{11}$) was



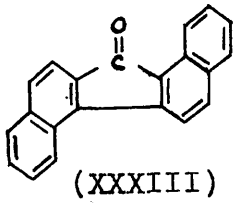
(XXX)



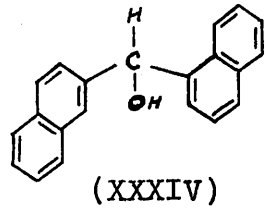
(XXXI)



(XXXII)



(XXXIII)



(XXXIV)

isolated by distillation. Sulphuric acid ring closure of the corresponding acid (XXXII; R=H) readily yielded 1:2:5:6-dibenzfluorenone (XXXIII) from which the hydrocarbon (X) was obtained by heating with hydrazine hydrate, but not by the Clemmensen method of reduction.

Martin[31] has also prepared 1:2:5:6-dibenzfluorene by the dehydration of 1:2'-dinaphthylcarbinol (XXXIV) with metaphosphoric acid but the yield of hydrocarbon was too small for the method to be of practical value.

The 1:2:5:6-dibenzfluorene and 1:2:5:6-dibenzfluorenone used in this investigation were prepared by the method of Swain and Todd.

Treatment of a suspension of 1:2:5:6-dibenzfluorene in acetic acid with twice the theoretical quantity

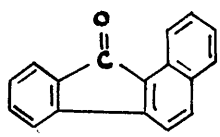
of fuming nitric acid led to the formation of a mononitro derivative which was readily reduced to the corresponding amino-1:2:5:6-dibenzfluorene by stannous chloride and hydrochloric acid.

By analogy with the behaviour of naphthalene and of fluorene it is considered probable that in substitution reactions 1:2:5:6-dibenzfluorene is attacked in the 7-position, which is, at the same time, the only available 2-position of the fluorene residue and an α-position of a naphthalene nucleus. Unfortunately failure has attended all attempts to convert the above amine, by diazotisation and by hydrolysis under pressure with dilute sulphuric acid, to a phenol for comparison with 7-hydroxy-1:2:5:6-dibenzfluorene. The synthesis of 7-hydroxy-1:2:5:6-dibenzfluorene is described later. We have also failed to obtain 7-amino-1:2:5:6-dibenzfluorene from the 7-hydroxy compound by the action of ammonia in the presence of sodium bisulphite and dioxan; a method similar to that used by Fieser and his collaborators[32] for the conversion of 3- and 8-hydroxy-1:2-benzanthracene into the corresponding amines.

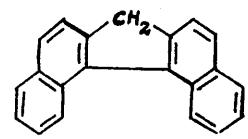
Sulphonation of 1:2:5:6-dibenzfluorene has been accomplished by adoption of the procedure employed by Windaus and Rennhak[33] for the preparation of 3:4-benzpyrene-monosulphonic acid. 1:2:5:6-Dibenzfluorenesulphonic

acid is slightly soluble in hot water from which solution the sodium salt is precipitated on addition of a slight excess of sodium hydroxide. Both the acid and the sodium salt darken rapidly on exposure to light.

A mononitro derivative of 1:2:5:6-dibenzfluorenone has been prepared by adding fuming nitric acid to a suspension of the ketone in acetic acid. The same material was obtained by heating nitro-1:2:5:6-dibenzfluorene with selenious acid under pressure, but could not be isolated from the products of auto-oxidation by means of potassium methoxide in acetone solution. The former method of oxidation was first applied to compounds of this type by Badger[34] who employed it successfully for the preparation of 1:2-benzfluorenone (XXXV) and 1:2:5:6-dibenzfluorenone and it has recently been used by Martin[31] for the oxidation of 3:4:5:6-dibenzfluorene (XXXVI) to the corresponding

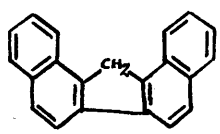


(XXXV)

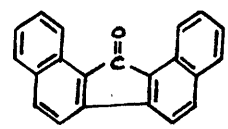


(XXXVI)

ketone. The auto-oxidisability of dibenzfluorenes was utilised by Tschitschibabin[35] and by Wanscheidt[36] for



(XXXVII)

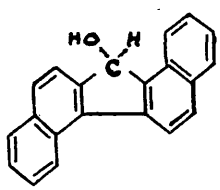


(XXXVIII)

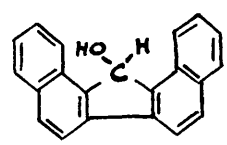
the conversion of 1:2:7:8-dibenzfluorene (XXXVII) into 1:2:7:8-dibenzfluorenone (XXXVIII). It has been our experience that several derivatives of 1:2:5:6-dibenzfluorene tend to revert to the corresponding ketone derivatives in alcoholic alkaline solution.

The preparation of amino-1:2:5:6-dibenzfluorenone by refluxing a suspension of the nitro compound in acetic acid with stannous chloride and hydrochloric acid was not successful. However, the compound has been obtained by boiling a solution of stannous chloride in hydrochloric acid for 20 hours under a solution of the nitrodibenzfluorenone in xylene.

9-Hydroxy-1:2:5:6-dibenzfluorene (XXXIX) is readily prepared by the action of zinc on a solution of the ketone in acetic acid. This method of reduction was used by Wanscheidt[36] for the conversion of 1:2:7:8-dibenzfluorenone (XXXVIII) into the carbinol (XL). Treatment of



(XXXIX)

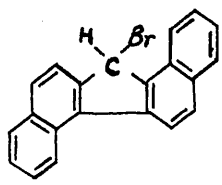


(XL)

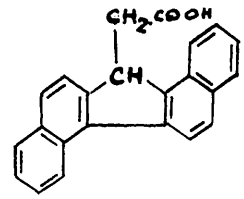
an acetic acid solution of 9-hydroxy-1:2:5:6-dibenzfluorene with hydrogen bromide produced 9-bromo-1:2:5:6-dibenzfluorene (XLI). On a larger scale the bromo

compound was obtained directly from 1:2:5:6-dibenzfluorenone without isolation of the intermediate carbinol.

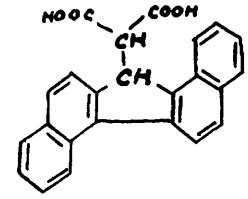
An attempt to prepare 1:2:5:6-dibenzfluorene-9-acetic acid (XLII) by condensation of the bromodibenzfluorene with diethyl malonate followed by decarboxylation of the dibasic acid (XLIII) proved fruitless although



(XLI)

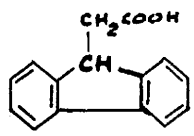


(XLII)

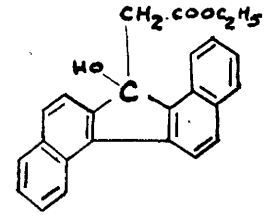


(XLIII)

this method has recently been used by Bachmann and Sheehan[37] for the production of fluorene-9-acetic acid (XLIV). 1:2:5:6-Dibenzfluorene-9-acetic acid (XLII) was readily obtained, however, by the action of hydriodic



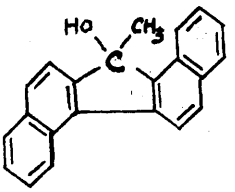
(XLIV)



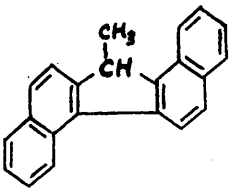
(XLV)

acid on an acetic acid solution of crude ethyl 9-hydroxy-1:2:5:6-dibenzfluorene-9-acetate (XLV). The latter compound arose from the Reformatsky reaction of ethyl bromacetate on 1:2:5:6-dibenzfluorenone.

9-Methyl-9-hydroxy-1:2:5:6-dibenzfluorene (XLVI) has been prepared by the action of methylmagnesium iodide



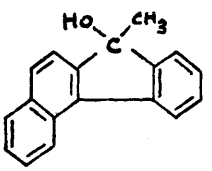
(XLVI)



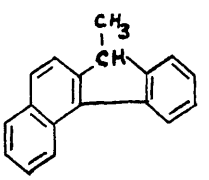
(XLVII)

on the dibenzfluorenone in the usual way. The carbinol was reduced by boiling with hydriodic acid in acetic acid to 9-methyl-1:2:5:6-dibenzfluorene (XLVII). This hydrocarbon sublimes unchanged and forms a bis-1:3:5-trinitrobenzene complex which crystallises from cyclohexane containing a little benzene but tends to dissociate in polar solvents. The picrate of 9-methyl-1:2:5:6-dibenzfluorene could not be isolated although a red colouration was obtained on rapidly evaporating to dryness a solution of the hydrocarbon and picric acid (two parts) in alcohol.

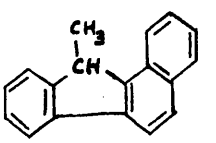
Fieser and Joshel[38] converted 9-methyl-9-hydroxy-3:4-benzfluorene (XLVIII) to 9-methyl-3:4-benzfluorene (XLIX) by dehydrating the carbinol with boiling acetic



(XLVIII)



(XLIX)

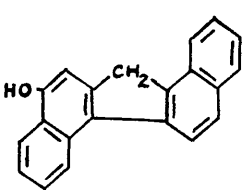


(L)

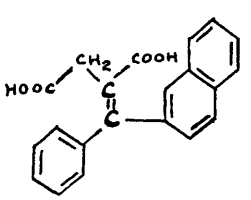
acid and hydrogenating in the presence of platinum catalyst and Badger[34] recently prepared 9-methyl-1:2-benzfluorene (L) by a similar process. When this method was applied to 9-methyl-9-hydroxy-1:2:5:6-dibenzfluorene the product could neither be crystallised nor sublimed and is considered to be a polymer.

In the presence of aluminium chloride 1:2:5:6-dibenzfluorene condensed readily, in nitrobenzene solution, with acetyl chloride to form a monoacetyl derivative. The method is similar to that used by Mosettig and van de Kamp[39] for the acetylation of phenanthrene.

In view of the probability discussed above that in substitution reactions 1:2:5:6-dibenzfluorene is attacked in the 7-position it was considered desirable to synthesise for comparison a 7-substituted 1:2:5:6-dibenzfluorene by a method which would establish its constitution. Consideration of the formula of 7-hydroxy-1:2:5:6-dibenzfluorene (LI) suggested the possibility of preparing the corresponding fluorenone by double cyclization of



(LI)

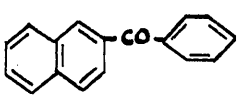


(LII)

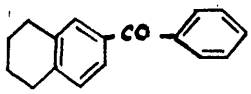
α-2-naphthyl-α-phenylitaconic acid (LII), the mono ester

of which would arise by the condensation of 2-benzoyl-naphthalene (LIII) and diethyl succinate in presence of sodium ethoxide.

2-Benzoylnaphthalene[40] (LIII) is readily obtained by sulphur dehydrogenation of 2-benzoyl-5:6:7:8-tetra-hydronaphthalene (LIV) which is easily prepared by the



(LIII)



(LIV)

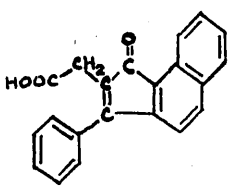
action of benzoyl chloride on tetralin in the presence of aluminium chloride[41]. In Friedel-Craft reactions tetralin substitutes exclusively in the 2-position of the aromatic nucleus.

Shortly after the synthesis of 7-hydroxy-1:2:5:6-dibenzfluorene had been devised, Dr. C.L. Hewett kindly placed at our disposal an unpublished account of the preparation of the acid (LII) by the method we had in mind.

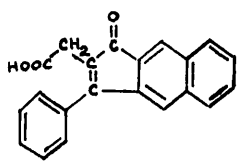
By the action of diazomethane on (LII) Hewett obtained a dimethyl ester m.p. 94-95°. This result has been confirmed by us and we have prepared, by the Fischer method of esterification, a second dimethyl ester m.p. 125-126°, the production of which was probably due to cis-trans isomerisation of the acid. On attempting to

repeat this preparation on a larger scale the ester m.p. 94° was obtained and it was unaltered on long boiling in methyl alcoholic solution saturated with hydrogen chloride.

The anhydride of (LII) on treatment with aluminium chloride in nitrobenzene solution was converted into a mixture of 1-keto-3-phenyl-6:7-benzindene-2-acetic acid (LV) and 1-keto-3-phenyl-5:6-benzindene-2-acetic acid (LVI). Mono ring-closure of unsaturated dibasic acids

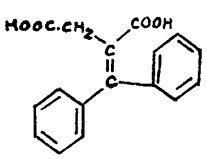


(LV)

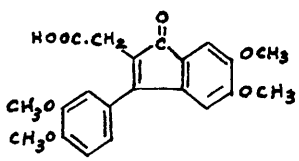


(LVI)

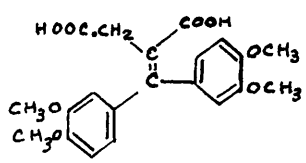
of this type involves the carboxyl group adjacent to the double bond. Thus Stobbe and Viewig[42] showed that diphenylitaconic acid (LVII) was converted into an orange indone derivative on treatment with cold sulphuric acid and Haworth and Sheldrick[43] prepared 1-keto-5:6-dimethoxy-3-(3':4'-dimethoxyphenyl)indene-2-acetic acid (LVIII) by the action of aluminium chloride on the anhydride



(LVII)



(LVIII)

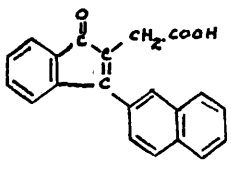


(LIX)

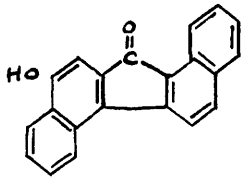
of the acid (LIX). The colours of the acids (LV) and (LVI) are consistent with the suggested indone structures.

Crystallisation from water of the sodium salt of the acid portion of the cyclisation product gave the sodium salt of an acid m.p. 176-177°. The isolation of the isomer, m.p. 153°, was accomplished by crystallising from water the potassium salt of the material contained in the liquor from the first crystallisation.

There are three possible keto-indene structures for these two acids (LV), (LVI) and (LX). The acid,



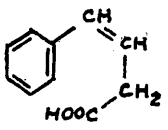
(LX)



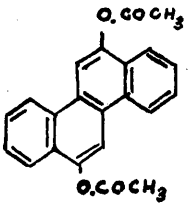
(LXI)

m.p. 176°, proved to have the structure (LV) since it underwent ring-closure in acetic anhydride solution to the acetate of 7-hydroxy-1:2:5:6-dibenzfluorenone (LXI) which yielded on zinc dust distillation a small quantity of 1:2:5:6-dibenzfluorene identical with an authentic specimen.

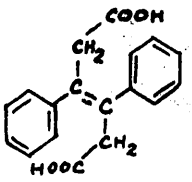
Numerous derivatives of β-benzylidenepropionic acid (LXII) have been cyclized to phenolic esters by the action of acid anhydrides. Beschke[44] prepared 2:8-diacetoxychrysene (LXIII) by treatment of the dibasic acid (LXIV) with a mixture of acetic anhydride and concentrated sulphuric acid and Bateman and Robinson[45]



(LXII)

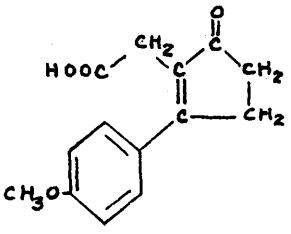


(LXIII)

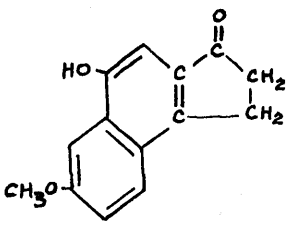


(LXIV)

used acetic anhydride (and propionic anhydride) as the condensing agent in the conversion of the acid (LXV) into the acetate (and propionate) of 4-hydroxy-3'-



(LXV)

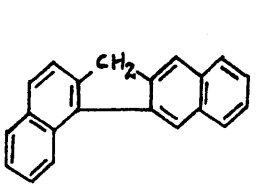


(LXVI)

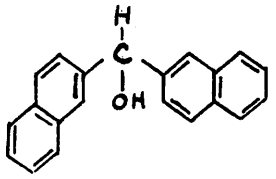
keto-6-methoxy-1:2-cyclopentenonaphthalene (LXVI).

A substance, m.p. 189°, was obtained on zinc dust distillation of the phenolic ketone which arose on hydrolysis of the acetate produced by acetic anhydride ring-closure of the acid m.p. 153°. Auto-oxidation of this substance, by means of potassium methylate in acetone solution, yielded a crude material melting at 155°. These constants are in fairly good agreement with those of 2:3:5:6-dibenzfluorene (LXVII) (m.p. 190·5°, corr.),

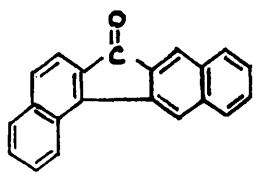
which Schmidlin and Huber[46] isolated as a by-product in the preparation of di-2-naphthylcarbinol (LXVIII), and



(LXVII)

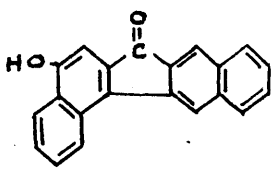


(LXVIII)

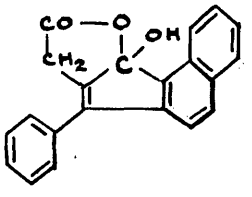


(LXIX)

2:3:5:6-dibenzfluorenone (LXIX) (m.p. 163-165°, cor.). This suggests that the phenolic ketone is 7-hydroxy-2:3:5:6-dibenzfluorenone (LXX) and that the acid, m.p. 153°, has the structure (LVI), which was expected in view of the general experience that a naphthalene nucleus enters into a cyclization reaction more readily than a benzene ring.



(LXX)

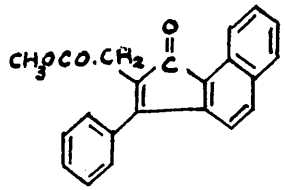


(LXXI)

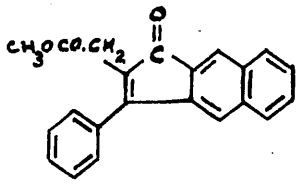
Two neutral substances were isolated from the products of ring-closure (LII) and one of these has been identified with the lactone, probably (LXXI), which Hewett obtained by sulphuric acid treatment of the acid.

The isomeric acids (LV) and (LVI) each give rise to two distinct methyl esters; one by the action of

diazomethane on the acid and a second by the Fischer method of esterification. The products of the former method of esterification are believed to be the normal esters (LXXII) and (LXXIII) whereas the esters obtained by the action of

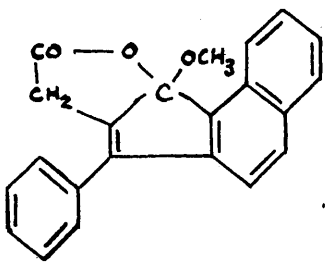


(LXXII)

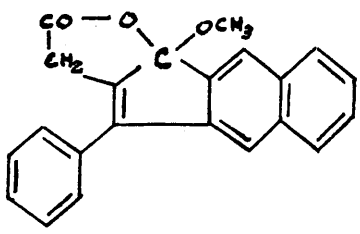


(LXXIII)

methyl alcoholic hydrogen chloride are considered to have the pseudo ester structures (LXXIV) and (LXXV). These

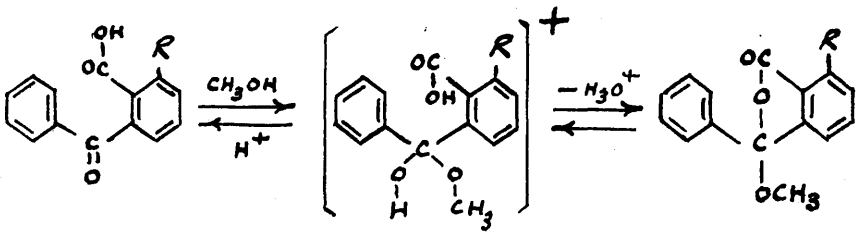


(LXXIV)



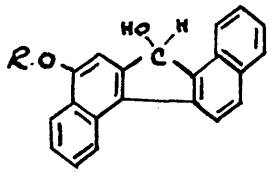
(LXXV)

formulae would be in agreement with the conclusions reached by Newman and McCleary[47] from a study of the esterification of derivatives of 2-benzoylbenzoic acid (LXXVI , R = H). These workers have found that by the Fischer method of esterification 6-substituted 2-benzoylbenzoic acids (LXXVI) produce pseudo esters, the formation of which they consider to proceed via the intermediate hemi-ketols of the structure shown.

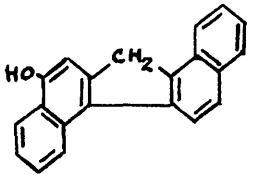


(LXXVI) hemi-ketol pseudo ester

Treatment of 7-hydroxy-1:2:5:6-dibenzfluorenone (LXI) with zinc and acetic acid gave 7:9-dihydroxy-1:2:5:6-dibenzfluorene (LXXVII, R = H) which was reduced directly to 7-hydroxy-1:2:5:6-dibenzfluorene (LXXVIII) by the action of hydriodic acid. The phenol (LXXVIII) was also obtained in a similar manner from the acetate of (LXI), the hydriodic acid hydrolysing the



(LXXVII)



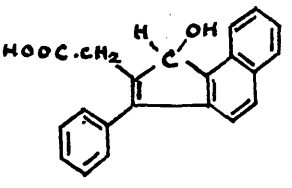
(LXXVIII)

ester grouping of the intermediate 7-acetoxy-9-hydroxy-1:2:5:6-dibenzfluorene (LXXVII; R = CH_3CO). 7-Hydroxy-1:2:5:6-dibenzfluorene is insoluble, or very slightly soluble, in aqueous alkali, and in alcoholic alkaline solution is rapidly auto-oxidised to 7-hydroxy-1:2:5:6-dibenzfluorenone. It cannot be methylated in ethereal

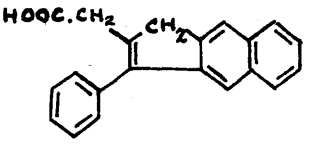
solution by the action of diazomethane, but the methoxy derivative is produced on addition of methyl sulphate and alcoholic potash in an atmosphere of hydrogen to a solution of the phenol in alcohol.

Reduction of 1-keto-3-phenyl-6:7-benzindene-2-acetic acid (LV) by the Clemmensen and by the zinc-acetic acid-hydriodic acid methods gave the same material which is readily soluble in cold sodium carbonate solution and analyses for a compound $C_{21}H_{16}O_3$. The analysis of the methyl ester is consistent with this formula. It is probable that the product is 1-hydroxy-3-phenyl-6:7-benzindene-2-acetic acid (LXXIX), although this is surprising in view of the facility with which 9-hydroxy-dibenzfluorene derivatives are reduced by hydriodic acid. The structure of this compound is being investigated further.

Clemmensen reduction of the isomeric 1-keto-3-phenyl-5:6-benzindene-2-acetic acid (LVI) proceeded in the normal manner to give 3-phenyl-5:6-benzindene-2-acetic acid (LXXX).



(LXXIX)



(LXXX)

EXPERIMENTAL.

Nitro-1:2:5:6-dibenzfluorene. A mixture of nitric acid (0.63 c.c.; 2 mols.; d = 1.50) and glacial acetic acid (5 c.c.) was added dropwise to a well stirred suspension of 1:2:5:6-dibenzfluorene (4 g.) in glacial acetic acid (50 c.c.). After standing for one hour the brownish solid was removed and washed first with acetic acid and then with methyl alcohol. Crystallisation from xylene gave orange needles of nitro-1:2:5:6-dibenzfluorene (3.5 g.; yield 75%) melting at 184-185°. (Found: C, 81.00; H, 4.07; N, 4.70. $C_{21}H_{13}O_2N$ requires C, 81.03; H, 4.18; N, 4.50%).

Amino-1:2:5:6-dibenzfluorene. A suspension of the above nitro compound (3 g.) in boiling glacial acetic acid (120 c.c.) was treated slowly with a solution of stannous chloride (10 g.) in concentrated hydrochloric acid (40 g.). The mixture was refluxed for one hour (colour changed to yellow-grey) and the solid was removed, washed, and boiled for an hour with dilute sodium hydroxide solution (15 g. NaOH in 200 c.c.). The insoluble amine was filtered, dried and crystallised from benzene in buff coloured needles (2 g.; yield, 74%), darkening at 215° and melting at 242-246°.

A small quantity was sublimed at 180° in high vacuum and recrystallised from benzene. Yellowish needles, m.p. 245-249°, sintering 241°. (Found: C, 89.67; H, 5.42; N, 5.23. $C_{21}H_{15}N$ requires C, 89.68; H, 5.34; N, 4.98%).

Diacetyl amine. A solution of the above amine (0.1 g.) in acetic anhydride (3 c.c.) was boiled under reflux for 10 minutes, and on cooling the diacetyl derivative separated out. It recrystallised from ethyl acetate in brownish prisms, m.p. 245-250° (dec.). (Found: C, 82.09; H, 5.56. $C_{25}H_{19}O_4N$ requires C, 82.19; H, 5.21%).

Attempted conversions of the above amine into hydroxy-1:2:5:6-dibenzfluorene.

1. Cf. Preparation of 2:6-dichloro-4-nitrophenol (de Milt and van Zandt, J.A.C.S., 1936, 58, 2044) and of 4-hydroxy-9:10-dihydrophenanthrene (Krueger and Mosettig, J. Org. Chem., 1938, 3, 340).

A solution of nitrosylsulphuric acid was prepared by adding sodium nitrite (0.2 g.) to an ice-cold mixture of water (1 c.c.) and concentrated sulphuric acid (8 c.c.) and then warming carefully to 40° till a clear solution resulted.

Amino-1:2:5:6-dibenzfluorene (0.3 g.) in cold pyridine (10 c.c.) was added slowly, with stirring, to the nitrosylsulphuric acid, the temperature of which was kept below 0° (addition took about 3 hours). The mixture was stirred at this temperature for a further ½ hour and poured into 40 c.c. of ice-water. Urea (0.2 g.) was added and after 30 minutes the insoluble material was removed by filtration. The filtrate on being heated on the water bath yielded only a trace of precipitate which could not be further investigated. A suspension of the insoluble material in 200 c.c. of water, containing 10 c.c. of concentrated sulphuric acid, was heated on the water bath for an hour. The mixture was again filtered and the residue extracted with hot benzene (charcoal) but from the benzene extract only a small quantity of black tarry material was obtained.

2. To a well stirred suspension of the amine (0.2 g.) in water (75 c.c.), cooled to 0°, concentrated hydrochloric acid (1 c.c.) was added followed by sodium nitrite (0.1 g.). After 1½ hours (colour had changed from yellow to brown) urea (0.25 g.) was added and the mixture was heated slowly to the boiling point and filtered. The residue was completely insoluble in hot

dilute alkali and was dissolved in hot benzene (charcoal). The dark sticky material obtained on removal of the benzene under reduced pressure could not be crystallised and was not further examined.

3. Sodium nitrite (0.05 g.) was added slowly to an ice-cold solution of aminodibenzfluorene (0.2 g.) in concentrated sulphuric acid (8 c.c.). The solution was warmed gradually to 60° and maintained at that temperature for 10 minutes, at the end of which 30 c.c. of water were added. The insoluble material obtained on heating the mixture for an hour on the steam bath was soluble in dilute sodium hydroxide solution, slightly soluble in hot water, but insoluble in non-polar solvents and is considered to be a sulphonic acid.

4. Cf. Preparation of 6-hydroxychrysene (Newman and Cathcart, J. Org. Chem., 1940, 5, 621).

A suspension of the amine (0.2 g.) in 10% sulphuric acid (2 c.c.) was heated in a sealed tube for 18 hours at 190°. The sublimate (6 mg.) obtained by heating the partly charred product at 220° under a pressure of 0.2 mm. darkened rapidly on exposure to air and melted slowly with decomposition above 200°. It is probably a product of sulphonation. The melting point

was depressed on admixture with synthetic 7-hydroxy-1:2:5:6-dibenzfluorene.

Complete decomposition resulted when the experiment was carried out by heating for 6 hours at 240-250°.

1:2:5:6-Dibenzfluorene-sulphonic acid. To an ice-cold suspension of 1:2:5:6-dibenzfluorene (3 g.) in acetic anhydride (150 c.c.) 18 c.c. of a mixture of 2 c.c. concentrated sulphuric acid in 20 c.c. of acetic anhydride were added slowly with stirring. After standing overnight in the refrigerator the insoluble material (2.9 g.) was removed and washed with dry ether. The sulphonic acid crystallised from acetic acid, with slight decomposition, in greenish needles and from ethyl acetate in colourless needles m.p. 112-120° (dec.). (Found: C, 72.72; H, 4.14. $C_{21}H_{14}O_3S$ requires C, 72.83; H, 4.05%). The acid decomposes on standing.

The sodium salt was precipitated from a hot aqueous solution of the sulphonic acid by addition of a slight excess of sodium hydroxide solution. It is slightly soluble in hot but insoluble in cold water and darkens on exposure to light.

Attempted preparations of nitro-1:2:5:6-dibenzfluorenone.

1. A mixture of fuming nitric acid (0.2 c.c.; d = 1.50) and glacial acetic acid (1.5 c.c.) was added slowly with stirring to a suspension of 1:2:5:6-dibenzfluorenone (0.5 g.) in acetic acid (5 c.c.) at the ordinary temperature. After stirring for 2 hours the insoluble material was removed, dried, and found to be unchanged dibenzfluorenone.

2. Finely ground 1:2:5:6-dibenzfluorenone (0.4 g.) was dusted on to ice-cold fuming nitric acid (2 c.c.) in which it dissolved slowly. When the addition was complete, the solution was poured on to ice-water and the orange precipitate, which came down, was removed and dried. The material, m.p. 190-210°, could not be crystallised from the ordinary solvents and is probably a polynitro-compound. An attempt was made to reduce it to an amine as follows:-

A suspension of the nitro-compound (0.2 g.) in boiling glacial acetic acid (8 c.c.) was treated with a solution of stannous chloride (1 g.) in concentrated hydrochloric acid (4 c.c.). After boiling for 10 minutes (solid darkened considerably and tended to tar) the mixture was poured into a large excess of hot concentrated

sodium hydroxide solution and the black insoluble material removed and dried. It was insoluble in the usual solvents and was not examined further.

Nitro-1:2:5:6-dibenzfluorenone.

Fuming nitric acid (0.6 c.c.; d = 1.50) was added dropwise to a well-stirred suspension of 1:2:5:6-dibenzfluorenone (0.5 g.) in glacial acetic acid (8 c.c.). After ten minutes the solid was removed, dried and crystallised from much xylene in red needles (0.5 g.) m.p. 312-319°. For analysis, a small quantity was crystallised several times from xylene and from dioxan giving fine red needles melting at 324-326°. (Found: N, 4.31. $C_{21}H_{11}O_3N$ requires N, 4.31%).

Amino-1:2:5:6-dibenzfluorenone.

A mixture of a solution of the above nitro compound (0.3 g.) in xylene (100 c.c.) and a solution of stannous chloride (6 g.) in concentrated hydrochloric acid (60 c.c.) was refluxed for 20 hours. The insoluble tin complex was decomposed by boiling with concentrated alkali, filtered, and the residue crystallised from xylene in black needles (0.12 g.) m.p. 265-270°. (Found: C, 85.55; H, 4.83. $C_{21}H_{13}ON$ requires C, 85.42; H, 4.41%).

Oxidation of nitro-1:2:5:6-dibenzfluorene.

1. A solution of potassium methylate (from 0.5 g. of potassium) in methyl alcohol (1.5 c.c.) was added to a boiling suspension of nitrodibenzfluorene (0.5 g.) in acetone (30 c.c.). An intense violet colour was produced and the nitro-compound went into solution. The boiling was continued for ten minutes after which the solvent was allowed to evaporate but no crystalline material could be obtained from the dark residual tar.

2. Nitro-1:2:5:6-dibenzfluorene (0.16 g.) was heated in a sealed tube at 230° for 6 hours with a solution of selenium dioxide (0.3 g.) in water (0.3 c.c.). The product, after several crystallisations from xylene, separated in red needles (0.05 g.) m.p. 308-312°. The melting point was not depressed by mixing with the nitro derivative (m.p. 324-326°) obtained by direct nitration of 1:2:5:6-dibenzfluorenone.

9-Hydroxy-1:2:5:6-dibenzfluorene (XXXIX).

1:2:5:6-Dibenzfluorenone (2 g.) was reduced in glacial acetic acid solution (200 c.c.) by boiling for 45 minutes with zinc filings (2 g.). The carbinol was precipitated on addition of water and crystallised from

benzene in very pale yellow, almost colourless, needles (1.5 g.) m.p. 201-202°. (Found: C, 89.22; H, 4.91. $C_{21}H_{14}O$ requires C, 89.36; H, 4.96%).

9-Bromo-1:2:5:6-dibenzfluorene (XLI).

1. A hot solution of 9-hydroxy-1:2:5:6-dibenzfluorene (0.1 g.) in glacial acetic acid (10 c.c.) was saturated with hydrogen bromide. On cooling the bromo compound separated and was recrystallised from benzene in yellow needles melting at 197-199°. (Found: Br, 23.40. $C_{21}H_{13}Br$ requires Br, 23.19%).

2. 1:2:5:6-Dibenzfluorenone (2.5 g.) was boiled in glacial acetic acid solution (250 c.c.) with zinc filings (3 g.) for an hour. The hot filtrate was saturated with hydrogen bromide and on cooling the mixture was poured into a large volume of ice-water. The precipitate, on crystallisation from benzene (charcoal), gave 9-bromo-1:2:5:6-dibenzfluorene (2.1 g.; yield 68%).

Attempted preparation of 1:2:5:6-dibenzfluorene-9-acetic acid.

A solution of 9-bromo-1:2:5:6-dibenzfluorene (0.5 g.) in dry benzene (50 c.c.) was added to a chilled solution of sodio-malonic ester, prepared from 0.2 g. of

sodium, 2 c.c. of diethyl malonate and 15 c.c. of absolute alcohol, in an atmosphere of nitrogen. The mixture was refluxed for 2 hours and the oily residue obtained on removal of the solvents was boiled in alcoholic potash solution, poured into water and acidified. The colourless precipitate was dried and heated at 180° for 45 minutes, when a red oil was produced. On cooling the oil solidified to a dark red substance which was completely insoluble in warm dilute alkali. A small quantity of this material was sublimed in high vacuum at 130° and crystallised from alcohol in red needles, m.p. 153-156°.

1:2:5:6-Dibenzfluorene-9-acetic acid (XLII).

Pure zinc filings (2.5 g.) were added to a mechanically stirred solution of 1:2:5:6-dibenzfluorenone (1.5 g.) in dry benzene (150 c.c.) containing ethyl bromacetate (4 c.c.) and pyridine (1 c.c.) and the mixture was refluxed until the reaction started. No reaction took place in the absence of pyridine. After boiling gently for a further 1½ hours the benzene solution was decanted into ice and dilute sulphuric acid. The benzene layer was separated, dried, and the solvent removed. Attempted hydrolysis at this stage by means of alcoholic

potash resulted in the carbinol ester being auto-oxidised to dibenzfluorenone and the ester was converted without purification to 1:2:5:6-dibenzfluorene-9-acetic acid by boiling for 2 hours in acetic acid solution (40 c.c.) containing hydriodic acid (5 c.c.; d = 1.95). The acid was precipitated by pouring into ice-water containing sulphurous acid and crystallised from toluene in colourless needles (1.1 g.; yield 64%), m.p. 221-223°. (Found: C, 85.58; H, 5.49. $C_{23}H_{16}O_2$ requires C, 85.19; H, 4.94%).

The sodium salt is insoluble in cold but slightly soluble in hot water, from which it crystallises in micro-needles.

Methyl ester. The methyl ester, prepared by the action of diazomethane on an ethereal solution of the acid, crystallised from alcohol in pale yellow needles, m.p. 127-128°. (Found: C, 84.91; H, 5.34. $C_{24}H_{18}O_2$ requires C, 85.21; H, 5.33%).

Attempted preparation of 9-methyl-9-hydroxy-1:2:5:6-dibenzfluorene.

A solution of the Grignard reagent made from 0.24 g. of magnesium and 1.5 g. of methyl iodide in 20 c.c. of ether was added dropwise to a dry benzene solution (100 c.c.)

of 1:2:5:6-dibenzfluorenone (2 g.). After standing overnight at ordinary temperature the mixture was decomposed with ice-cold dilute sulphuric acid and extracted with benzene. On removal of the benzene the unchanged ketone was recovered.

9-Methyl-9-hydroxy-1:2:5:6-dibenzfluorene (XLVI).

To a Grignard solution prepared by the action of methyl iodide (4.5 g.) on magnesium (0.7 g.) in ether a solution of 1:2:5:6-dibenzfluorenone (2 g.) in dry benzene (100 c.c.) was added slowly with continuous stirring. After standing overnight at ordinary temperature the ether was removed and the benzene solution boiled under reflux for 2 hours. The cold solution was treated with ice-cold ammonium chloride solution and the benzene layer was separated, dried, and the solvent removed. The residual oil crystallised from a mixture of benzene and ligroin in yellow rectangular prisms (1.7 g.; 80%) melting at 131-132°. (Found: C, 89.18; H, 5.48. $C_{22}H_{16}O$ requires C, 89.19; H, 5.40%).

Attempted preparation of 9-methyl-1:2:5:6-dibenzfluorene.

The above carbinol (0.2 g.) was boiled for an hour in glacial acetic solution (15 c.c.), cooled and the solution shaken for 3½ hours with platinum catalyst (10 mg.) in an atmosphere of hydrogen. The yellow solid

obtained by pouring into water could neither be sublimed nor crystallised. It is probably a product of polymerisation.

9-Methyl-1:2:5:6-dibenzfluorene (XLVII).

A solution of the carbinol (1.4 g.) in glacial acetic acid (70 c.c.) containing hydriodic acid (7 g.; d = 1.95) was refluxed for 3 hours. The yellow precipitate produced on pouring the cold solution on to ice-cold dilute sulphurous acid was dried and sublimed at 120° in high vacuo. On crystallisation from absolute alcohol colourless plates of the hydrocarbon (1.2 g.; 90%) m.p. 144-145° were obtained. (Found: C, 94.34; H, 5.63. $C_{22}H_{16}$ requires C, 94.29; H, 5.71%).

The bis-1:3:5-trinitrobenzene complex was prepared in alcoholic solution and crystallised from cyclohexane containing a little benzene in orange needles, m.p. 139.5-140.5°. (Found: N, 12.13. $C_{22}H_{16}.2C_6H_3O_6N_3$ requires N, 11.90%).

Acetyl-1:2:5:6-dibenzfluorene.

1. A solution of 2 grams of aluminium chloride in nitrobenzene (20 c.c.) was added to 1:2:5:6-dibenzfluorene (2 g.) dissolved in nitrobenzene (10 c.c.), and to the resultant brown-red solution, cooled in ice, freshly

distilled acetyl chloride (0.7 c.c.) was added all at once. The mixture was stirred for 4 hours (1 hour in ice-water and 3 hours at room temperature) and allowed to stand for 16 hours at ordinary temperature. After decomposing in the usual way, with ice and hydrochloric acid, the nitrobenzene was removed in steam and the residue dissolved in chloroform. The material obtained from the dry chloroform solution on evaporation gave, after two crystallisations from benzene, acetyl-1:2:5:6-dibenzfluorene (1.2 g.; yield 52%) m.p. 142-143°.

For analysis a specimen was crystallised several times from benzene and then from alcohol giving straw coloured needles m.p. 146-146.5°. (Found: C, 89.44; H, 5.16. $C_{23}H_{16}O$ requires C, 89.62; H, 5.19%).

The oxime, prepared in pyridine solution, crystallised from benzene in straw coloured needles, m.p. 209-212°. (Found: C, 84.86; H, 5.63. $C_{23}H_{17}ON$ requires C, 85.45; H, 5.26%).

Methyl ester of γ-2-naphthyl-γ-phenylitaconic acid (LII).

A methyl alcoholic solution of the acid, saturated with dry hydrogen chloride, was boiled under reflux for 4 hours. The alcohol was removed under reduced pressure and the residue dissolved in ether. The oil obtained on evaporation of the ether solution, after washing with

sodium carbonate solution and drying, crystallised from methyl alcohol in colourless plates m.p. 125-126°. (Found: C, 76.37; H, 5.61; OMe, 17.42. $C_{23}H_{20}O_4$ requires C, 76.67; H, 5.56; OMe, 17.22%).

On repetition of this work the dimethyl ester m.p. 94-95°, prepared by Hewett by treatment of the acid with diazomethane, was obtained. The ester, m.p. 94-95°, was recovered unchanged after boiling for 6 hours in methyl alcoholic solution saturated with hydrogen chloride.

Action of aluminium chloride on the anhydride of γ-2-naphthyl-δ-phenylitaconic acid (LII).

The acid (40 g.) was converted into the anhydride by refluxing with acetyl chloride (80 g.) for 2 hours followed by removal of the excess chloride.

Anhydrous aluminium chloride (40 g.) was added slowly to a solution of the anhydride in nitrobenzene (400 c.c.), cooled in ice-water, and after standing at 0° for 24 hours the mixture was decomposed in the usual way with ice and hydrochloric acid. The residue obtained after removal of the nitrobenzene in steam was dissolved in ether and extracted with a large volume of very dilute

sodium carbonate solution (about $\frac{1}{4}$N.). The carbonate solution was washed with ether and the sodium salts (24 g.) of the acids (LV) and (LVI) were precipitated therefrom by addition of sodium chloride.

The combined ethereal solutions were taken to dryness and the residue crystallised from benzene. A red solid (2 g.) m.p. 240-255° (dec.) separated but was not further investigated.

From the benzene liquor on standing colourless rectangular crystals were deposited. These were recrystallised several times from benzene and gave colourless needles m.p. 164.5-165.5°. (Found: C, 80.17; H, 4.32. $C_{21}H_{14}O_3$ requires C, 80.25; H, 4.46%). The melting point was not depressed on mixing with a specimen of 'Hewett's lactone' m.p. 166°.

1-Keto-3-phenyl-6:7-benzindene-2-acetic acid (LV).

The sodium salt mixture obtained as described above was recrystallised twice from water and the acid generated from the product crystallised from benzene in orange coloured needles (8.5 g.) m.p. 176-177°. (Found: C, 80.23; H, 4.32. $C_{21}H_{14}O_3$ requires C, 80.25; H, 4.46%).

Normal methyl ester.

A slight excess of diazomethane in ether was added to an ethereal solution of the acid. The material

obtained by removal of the solvent crystallised from methyl alcohol in red needles m.p. 136°. (Found: C, 80.41; H, 4.95. $C_{22}H_{16}O_3$ requires C, 80.49; H, 4.88%).

Pseudo methyl ester.

A solution of the acid (0.1 g.) in methyl alcohol (10 c.c.), saturated with dry hydrogen chloride, was boiled for 20 minutes. On cooling crystals were deposited and after recrystallisation from methyl alcohol bright red prisms (0.045 g.) m.p. 83.5-84.5° were obtained. (Found: C, 80.11; H, 5.25%).

1-Keto-3-phenyl-5:6-benzindene-2-acetic acid (LVI).

The material precipitated on addition of acid to the mother liquor of the sodium salt of (LV) could not be purified by crystallisation. It was converted into the potassium salt which after two crystallisations from water and acidification gave the acid (LVI) crystallising from benzene-cyclohexane in yellow prisms (6.5 g.) m.p. 150-153° after softening at 147°. (Found: C, 80.16; H, 4.32%).

Normal methyl ester.

Prepared in similar manner to normal ester of

isomeric acid. Yellow needles from methyl alcohol m.p. 98-99°. (Found: C, 80.45; H, 5.01%). This material would not crystallise from cyclohexane.

Pseudo methyl ester.

A methyl alcoholic solution of the acid was saturated with dry hydrogen chloride and refluxed for 3 hours. Most of the solvent was removed and the residue was dissolved in ether and the ethereal solution shaken with dilute sodium carbonate solution (some unchanged acid recovered). The material obtained on removal of the ether could not be crystallised from methyl alcohol but crystallised from cyclohexane in yellow needles m.p. 101.5-102.5°. (Found: C, 80.68; H, 5.01). A mixture with the above ester melted at 93-94°.

7-Acetoxy-1:2:5:6-dibenzfluorenone.

A solution of 1-keto-3-phenyl-6:7-benzindene-2-acetic acid (6 g.) in freshly distilled acetic anhydride (60 c.c.) was boiled for 15 minutes. The acetate (6.2 g.) which crystallised out on cooling was sufficiently pure for use in the next stage. For analysis a specimen was crystallised twice from acetic acid giving deep red

needles m.p. 245-246°. (Found: C, 81.31; H, 4.31. $C_{23}H_{14}O_3$ requires C, 81.66; H, 4.14%).

7-Hydroxy-1:2:5:6-dibenzfluorenone (LXI).

The above acetate (2.5 g.) was added to a solution of potassium hydroxide (1.8 g.) in methyl alcohol (90 c.c.) and the mixture boiled for about a minute. The resultant dark green solution was poured into a large volume of ice-water and the precipitate obtained on acidification was removed and dried. Crystallisation from alcohol (dark purple solution) gave black needles of the phenol (2.0 g.) which decomposed above 250° but had no definite melting point. (Found: C, 85.09; H, 4.27. $C_{21}H_{12}O_2$ requires C, 85.14; H, 4.05%).

7-Methoxy-1:2:5:6-dibenzfluorenone.

The methoxyl derivative was prepared by the action of excess methyl sulphate on a solution of the above phenol in alcohol containing potassium hydroxide. It crystallised from benzene in dark red, almost black, needles melting at 196-197°. (Found: C, 85.08; H, 4.76; OMe, 9.50. $C_{22}H_{14}O_2$ requires C, 85.16; H, 4.52; OMe, 10.00%).

Zinc dust distillation of 7-hydroxy-1:2:5:6-dibenzfluorenone.

An intimate mixture of 0.5 g. of the above phenol and 20 g. of zinc dust was heated to dull redness in an atmosphere of hydrogen till sublimation ceased. A solution of the sublimate in benzene-ligroin was passed down a tower of alumina, and the chromatograph was developed with pure benzene. The material obtained by removal of the solvent from the first fraction of the eluate crystallised from benzene-alcohol in almost colourless needles m.p. 170-173°, alone or mixed with an authentic specimen of 1:2:5:6-dibenzfluorene. The yield of hydrocarbon was very small.

7-Acetoxy-9-hydroxy-1:2:5:6-dibenzfluorene.

7-Acetoxy-1:2:5:6-dibenzfluorenone (0.1 g.) was reduced by boiling in acetic acid solution (10 c.c.) with zinc filings (0.1 g.) till the red colour was destroyed (about 1 hour). The white solid precipitated by decanting the cooled solution into a large volume of ice-water was removed, dried, and crystallised from alcohol in colourless needles m.p. 222° (dec.). (Found: C, 80.46; H, 4.90. $C_{23}H_{16}O_3$ requires C, 81.18; H, 4.71%).

7-Hydroxy-1:2:5:6-dibenzfluorene (LXXIII).

1. A solution of 7-hydroxy-1:2:5:6-dibenzfluorenone (0.1 g.) in glacial acetic acid (10 c.c.) was boiled for an hour with zinc filings (0.1 g.). The 7:9-dihydroxy-dibenzfluorene precipitated on decanting the acetic acid solution into water could not be crystallised from the usual solvents. It was converted to 7-hydroxy-1:2:5:6-dibenzfluorene by refluxing for 2 hours in acetic acid solution (5 c.c.) containing hydriodic acid (0.25 c.c.; d = 1.95). The cold solution was poured on to ice and sulphurous acid, and the phenol, which precipitated, was removed, dried and crystallised from benzene. The slightly greyish material was sublimed at 170° in high vacuum and recrystallised twice from benzene giving colourless plates which sublimed above 200° but had no sharp melting point. (Found: C, 89.51; H, 4.95. $C_{21}H_{14}O$ requires C, 89.36; H, 4.96%).

2. 7-Acetoxy-1:2:5:6-dibenzfluorenone (2.5 g.) was reduced in acetic acid solution by the action of zinc filings as described above. Hydriodic acid (8 c.c.; d = 1.95) was added to the solution, after decantation from the excess zinc, the mixture boiled for 2 hours and

the 7-hydroxy-1:2:5:6-dibenzfluorene worked up as before. Yield = 1.8 g. (86%).

7-Acetoxy-1:2:5:6-dibenzfluorene.

A solution of the phenol in freshly distilled acetic anhydride was boiled for a few minutes and on cooling the acetate crystallised out. Recrystallisation from alcohol gave colourless plates m.p. 164-165°. (Found: C, 85.04; H, 4.63. $C_{23}H_{16}O_2$ requires C, 85.19; H, 4.94%).

7-Methoxy-1:2:5:6-dibenzfluorene.

The methoxyl derivative was not produced on dusting the phenol into an ethereal solution of diazomethane.

A boiling solution of the phenol (100 mg.) in absolute alcohol (50 c.c.) in an atmosphere of hydrogen was treated alternately with alcoholic potassium hydroxide solution and with methyl sulphate until no green colour was apparent on addition of the alkali (in all 2.7 g. of methyl sulphate was used). Excess alcoholic potash was added followed by a large volume of water. The light blue precipitate was removed and after several crystallisations from benzene gave colourless prisms

m.p. 217-218°. (Found: C, 89.46; H, 5.47. $C_{22}H_{16}O$ requires C, 89.19; H, 5.40%).

Attempted preparation of 7-amino-1:2:5:6-dibenzfluorene.

A mixture of 7-hydroxy-1:2:5:6-dibenzfluorene (0.2 g.), sodium bisulphite (0.9 g.), dioxan (1.1 c.c.), concentrated ammonia solution (2.2 c.c.) and water (2.2 c.c.) was heated in a sealed tube at 190-200° for 10 hours. From a benzene solution of the dry product, filtered from some charred material, only unchanged 7-hydroxy-1:2:5:6-dibenzfluorene was obtained.

1-Hydroxy-3-phenyl-6:7-benzindene-2-acetic acid (LXXIV).

1. 1-Keto-3-phenyl-6:7-benzindene-2-acetic acid (0.5 g.) was reduced in toluene solution (50 c.c.) by boiling for 1½ hours with 50 c.c. of dilute hydrochloric acid (6N) and 2 grams of amalgamated zinc. Ether was added and the toluene layer was separated and shaken with dilute sodium carbonate solution. The oily precipitate obtained on acidification of the carbonate extract was dissolved in ether, dried, and the solvent removed. The residual oil crystallised from aqueous acetic acid, and then from a mixture of benzene and n-hexane in

colourless prisms m.p. 165-168°. The melting point was not depressed on mixing with the material prepared as described below.

The yield was very small on account of the large quantity of resinous substance produced.

2. A solution of the keto-acid (1 g.) in glacial acetic acid (50 c.c.) was refluxed with zinc filings (1 g.) until the orange colour had completely disappeared (about 10 mins.). Hydriodic acid (5 c.c.; d = 1.95) was added to the solution after decantation from the zinc and the mixture was boiled for 2 hours before being poured into a large volume of ice-water and treated with sulphurous acid. The precipitate was removed and on crystallisation from aqueous alcohol gave colourless needles (0.6 g.; yield 63%), melting at 170° after sintering at 158°. (Found: C, 80.33; H, 5.26. $C_{21}H_{16}O_3$ requires C, 79.75; H, 5.06%).

Methyl ester.

The methyl ester, prepared by the action of diazomethane on ethereal solution of the acid, crystallised from cyclohexane in colourless prisms m.p. 105-106°. (Found: C, 80.13; H, 5.80. $C_{22}H_{18}O_3$ requires C, 80.00; H, 5.45%).

7-Acetoxy-2:3:5:6-dibenzfluorenone.

A solution of 1-keto-3-phenyl-5:6-benzindene-2-acetic acid (1.4 g.) in freshly distilled acetic anhydride (14 c.c.) was boiled under reflux for 30 minutes. On cooling the acetate (1.45 g.; yield 96%) m.p. 200-203° separated out in yellow needles. For analysis a specimen was crystallised several times from toluene giving bright yellow needles m.p. 204-206°. (Found: C, 81.70; H, 4.20. $C_{23}H_{14}O_3$ requires C, 81.66; H, 4.14%).

7-Hydroxy-2:3:5:6-dibenzfluorenone (LXX).

The above acetate (1 g.) was hydrolysed by boiling for a few minutes in methyl alcohol (25 c.c.) containing potassium hydroxide (0.5 g.). The yellow needles dissolved slowly to a deep blue solution which was diluted with water and acidified. The flocculent precipitate on crystallisation from alcohol gave claret coloured needles of 7-hydroxy-2:3:5:6-dibenzfluorenone which melted slowly above 250°. The yield was theoretical. (Found: C, 85.15; H, 4.16. $C_{21}H_{12}O_2$ requires C, 85.14; H, 4.05%).

2:3:5:6-Dibenzfluorene. - Zinc dust distillation of 7-hydroxy-2:3:5:6-dibenzfluorenone.

A mixture of the phenolic ketone (0.5 g.) and zinc dust (30 g.) was heated to dull redness until the sublimation ceased. The zinc dust was extracted with acetone, filtered, and the solvent removed. The residue, together with the material which had sublimed, was dissolved in alcohol, boiled with charcoal, and filtered. On cooling greyish prisms m.p. 189° (softening 185°) separated but the quantity of material was insufficient for analysis.

2:3:5:6-Dibenzfluorenone.

The material obtained on evaporation of the mother liquor from the above crystallisation was dissolved in acetone (5 c.c.) and boiled for 10 minutes with a solution of potassium methoxide (from 0.02 g. of potassium and 0.1 c.c. of methyl alcohol). Water was added and the mixture was extracted with chloroform. The brown residue obtained on removal of the chloroform melted at 155° after crystallisation from alcohol.

3-Phenyl-5:6-benzindene-2-acetic acid (LXXV).

A solution of 1-keto-3-phenyl-5:6-benzindene-2-acetic acid (4 g.) in toluene (400 c.c.) was boiled for four hours with hydrochloric acid (400 c.c.; 6 N)

and amalgamated zinc (16 g.). 3-Phenyl-5:6-benzindene-2-acetic acid was precipitated on acidification of a dilute sodium carbonate extract of the toluene layer and crystallised from benzene in colourless needles (1.5 g.; yield 40%) m.p. 177-178°. (Found: C, 83.74; H, 5.44. $C_{21}H_{16}O_2$ requires C, 84.00; H, 5.33%).

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I N D E X.

Part I.

Page.

PART II.

Syntheses of 1:9-phenylenecarbazole.

C O N T E N T S.

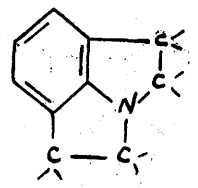
Part II.

INTRODUCTION.

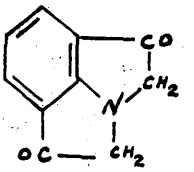
No tervalent nitrogen compound of the type $R_1R_2R_3N$ has been resolved into optically active isomers, the asymmetry of which is dependent solely on the non-planar distribution of the nitrogen valencies. It would appear, therefore, that either the valencies of the nitrogen atom have a planar distribution or that the enantiomorphic forms of the non-planar molecule are readily interconvertible.

Jackson and Kenner[1] suggested that positive evidence for the planar configuration of the nitrogen valencies would be supplied "by the preparation of a compound in the molecule of which a nitrogen atom is common to two ring structures, which are at the same time plane and coplanar." They continued thus: "Since, so far as we know, there is no evidence available which renders doubtful the plane configuration of five-membered ring structures, it would appear that these conditions would be fulfilled by a structure of type (I), if Kekulé's formula for benzene and its derivatives be accepted."

These workers failed to obtain the compound (II), which contains the basic structure (I), by the fusion



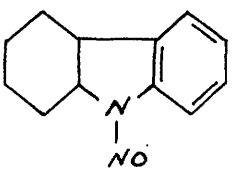
(I)



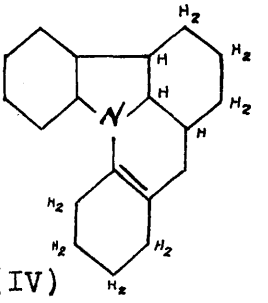
(II)

of sodium indoxylacetate with sodamide followed by treatment with methyl sulphate*.

Shortly before the appearance of Jackson and Kenner's paper Manjunath[2] reported the preparation of a compound $C_{18}H_{21}N$ by the action of zinc dust on an acetic acid solution of 9-nitrosohexahydrocarbazole (III) containing cyclohexanone. Manjunath represented this



(III)



(IV)

compound by the obviously incorrect formula (IV) which corresponds to $C_{19}H_{23}N$. We presume he intended his

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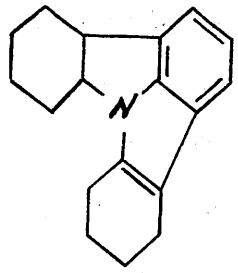
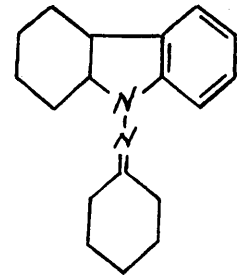
*Jackson and Kenner state that the composition of the product of this reaction "strangely enough, agreed with that of the compound sought in the experiment." Their analysis figures, however, agree with a substance $C_{10}H_{10}O_2N_2$, whereas the desired compound (II) has the molecular formula $C_{10}H_{10}O_2N$.

structural formula to be (V) which would be the normal

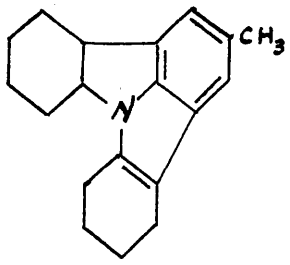


(V)

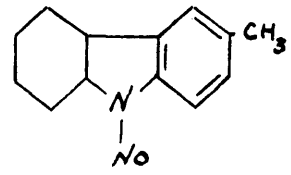


(VI)

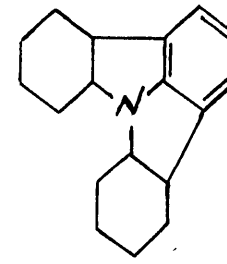
product of a Fischer indole ring closure of the intermediate hydrazone (VI). By a similar process the compound (VII) was obtained from a mixture of cyclohexanone and 6-methyl-9-nitrosohexahydrocarbazole (VIII).



(VII)



(VIII)



(IX)

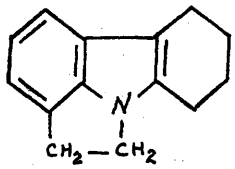
The molecules of the substances (V) and (VII) conform to the requirements of the structure (I) and should have planar configurations if the argument of Jackson and Kenner is sound. It is important, therefore, that Manjunath obtained a compound $C_{18}H_{23}N$, presumably (IX), by the electrolytic reduction of (V). The substance (IX), which still contains the structure (I),

is markedly basic and readily forms a crystalline hydrochloride and methiodide. It is probable that the distribution of the nitrogen valencies of these salts approaches that of tetrahedral configuration and it appears possible that non-planar structures of type (I) may exist and that the requirements postulated by Jackson and Kenner for planar distribution of the nitrogen valencies are invalid.

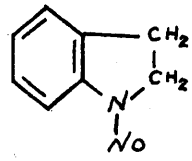
In the light of the electronic theory of valency, together with the recognition that tervalent sulphur compounds, $R_1R_2R_3S$, are resolvable, it would seem probable that the compounds $R_1R_2R_3N$ have a non-planar structure and that failure to resolve them into optically active isomers is due to the facility with which one enantiomorphic form passes into the other. Compounds containing the structure (I), however, would still be of vital theoretical importance if the plausible assumption is made that the enantiomorphic forms thereof be more stable than if the groups attached to the nitrogen atom are unconnected to one another.

Lions and Ritchie[3] have confirmed the preparation of the compounds (V) and (VII) and they have obtained

the substance (X), which they term 8:9-ethylene-1:2:3:4-tetrahydrocarbazole, by the reduction of 1-nitroso-



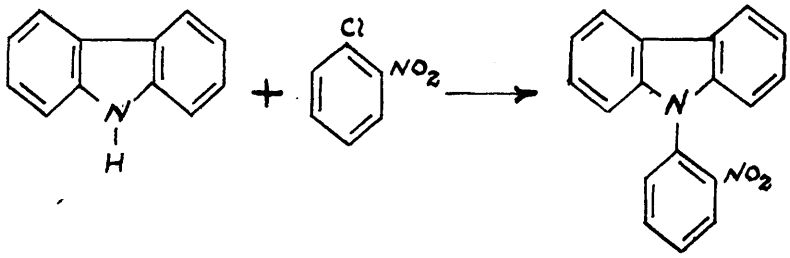
(X)



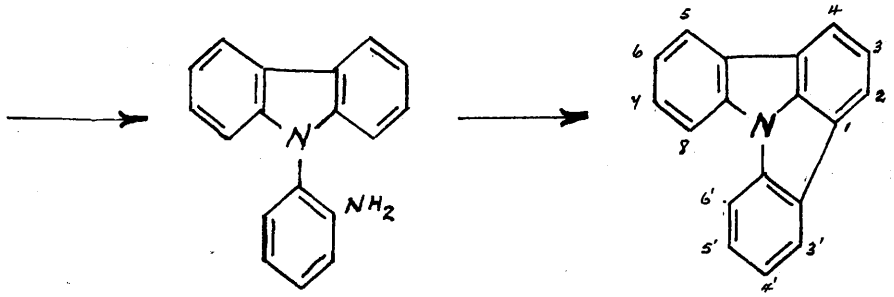
(XI)

indoline (XI) with zinc dust and acetic acid in presence of cyclohexanone.

1:9-Phenylenecarbazole (XIV), the parent substance of Manjunath's compounds, has been prepared by Dunlop and Tucker[4] by a Pschorr reaction on 9-(2'-aminophenyl)-carbazole (XIII). The amine (XIII) was obtained



(XII)

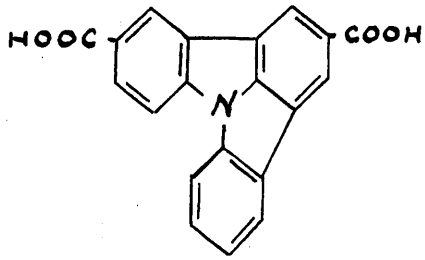


(XIII)

(XIV)

by stannous chloride reduction of 9-(2'-nitrophenyl)-carbazole (XII), which arose from the condensation of carbazole with o-nitrochlorobenzene in presence of potassium carbonate.

Consideration of the formula of 1:9-phenylene-carbazole (XIV) will show that substitution at any carbon atom other than position 3, will give rise to an asymmetric compound which should be resolvable into optically active forms. Dunlop and Tucker prepared several such derivatives, including 1:9-phenylenecar-bazole-3:6-dicarboxylic acid (XV). Attempts to resolve



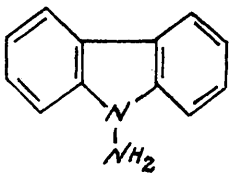
(XV)

this acid by crystallisation of alkaloidal salts were inconclusive on account of the ease with which the salts dissociated.

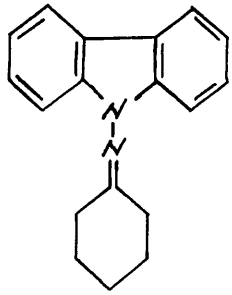
In view of the theoretical importance of 1:9-phenylenecarbazole (XIV) we considered it worth while

to attempt its synthesis by the two following methods:-

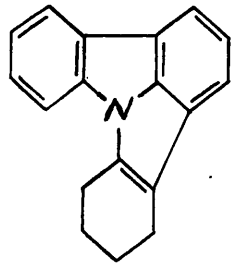
1). Indolisation of the cyclohexanone diphenylene-hydrazone (XVII) and dehydrogenation of 1:9-(3':4':-5':6'-tetrahydrophenylene)carbazole (XVIII) which would be produced.



(XVI)

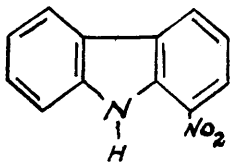


(XVII)

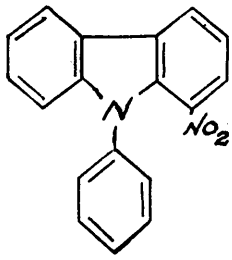


(XVIII)

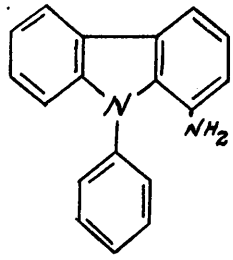
2). Condensation of 1-nitrocarbazole (XIX) with iodobenzene to 1-nitro-9-phenylcarbazole (XX) followed by a Pschorr reaction on the corresponding amine (XXI).



(XIX)



(XX)

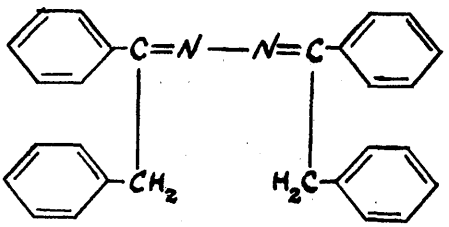


(XXI)

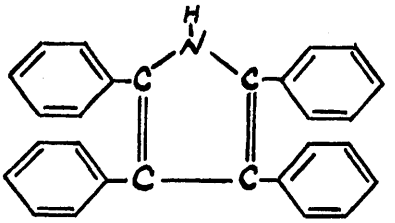
9-Aminocarbazole (XVI) was prepared by reduction of 9-nitrosocarbazole by the method of Wieland, Süsser and Fressel[5]. The condensation of 9-aminocarbazole

(XVI) with cyclohexanone(→ XVII) was accomplished by a slight modification of the procedure described by Manjunath[2].

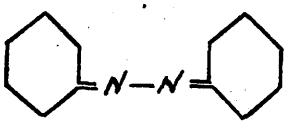
Removal of ammonia from the molecule of (XVII) was attempted by Manjunath but he obtained only "sticky uncrystallisable solids . . . . . which could not be purified." He gave no details of the methods employed. We have found that treatment of the hydrazene with mineral acids produced tarry solids, from which only carbazole could be isolated, and that long boiling in acetic acid solution gave 9-acetylaminocarbazole. When, however, a solution of the hydrazone in tetralin was treated at 165° with a saturated solution of hydrogen chloride in tetralin a small quantity of the required 1:9-(3':4':5':6'-tetrahydrophenylene)carbazole (XVIII) was obtained. This method of indolisation is similar to that used by Robinson and Robinson[6] to convert phenylbenzylketazine (XXII) into tetraphenylpyrrole (XXIII) and by Perkin and Plant[7] for the preparation of 1:2:3:4:5:6:7:8-octohydrocarbazole (XXV) from cyclohexylideneazine (XXIV).



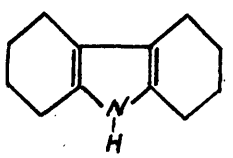
(XXII)



(XXIII)



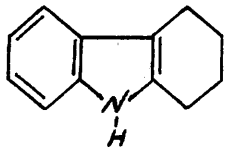
(XXIV)



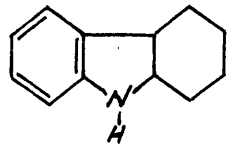
(XXV)

1:9-(3':4':5':6'-tetrahydrophenylene)carbazole is a colourless neutral substance, resembling 1:2:3:4-tetrahydrocarbazole. It forms a picrate and a 1:3:5-trinitrobenzene addition compound.

The conversion of tetrahydrophenylenecarbazole to 1:9-phenylenecarbazole (XIV) was readily accomplished by heating with sulphur in quinoline; a method used by Perkin and Plant[8] for the dehydrogenation of tetrahydrocarbazole (XXVI). In this connection it is surprising that Manjunath was unable to dehydrogenate the



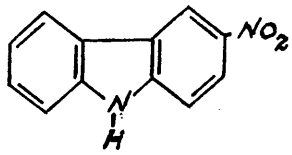
(XXVI)



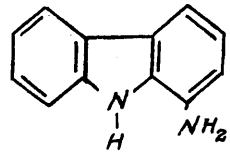
(XXVII)

compound (V) by treatment with sulphur in quinoline or with lead oxide (cf. Borsche, Witte and Bothe, Ann., 1908, 359, 73) although he found that hexahydrocarbazole (XXVII) was converted to carbazole by either of these methods.

Before attempting to synthesise 1:9-phenylenecarbazole by the second method mentioned above, we found it necessary to devise a new procedure for obtaining pure 1-nitrocarbazole in reasonable quantity. Direct nitration of carbazole gives chiefly 3-nitrocarbazole



(XXVIII)



(XXIX)

(XXVIII). A small quantity of 1-nitrocarbazole*, m.p.187°, was first isolated from the products of nitration of carbazole by Lindemann and Werther[9]. The structure of this compound was proved since its reduction product was identical with 1-aminocarbazole (XXIX) synthesised by a method which established its constitution[10]. The separation of 1-nitrocarbazole from 3-nitrocarbazole, however, has proved unusually difficult although Morgan and Mitchell[11] claim excellent results by fractional crystallisation followed by fractional sublimation. Repetition of Morgan and Mitchell's experiments gave us unsatisfactory results.

We have obtained 1-nitrocarbazole in fairly good yield by decarboxylation of 1-nitrocarbazole-3:6-dicarboxylic acid (XXX), the diethyl ester of which arose on nitration of the diethyl ester of carbazole-3:6-dicarboxylic acid (XXXI) in acetic acid solution. The ester was used on account of the very sparing solubility of the acid in organic solvents. Carbazole-3:6-dicarboxylic acid (XXXI) is readily prepared by the method of Dunlop and Tucker[4] by hydrolysis of 3:6-di-trichloracetylcarbazole (XXXII)

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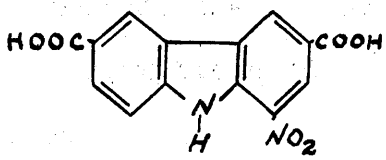
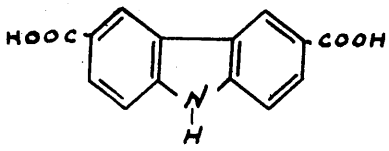
*The compound, m.p. 164°, alleged by Ziersch (Ber., 1909, 42, 3797) to be 1-nitrocarbazole, was shown by Morgan and Mitchell (J., 1931, 3283) to be a mixture of 1- and 3-nitrocarbazoles in approximately 1:1 molecular ratio.

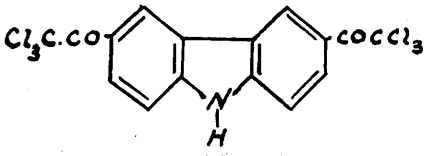
which is produced by the action of trichloracetonitrile



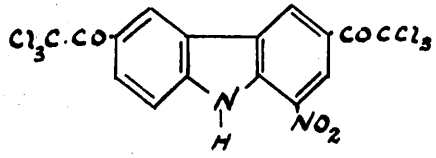
(XXX)



(XXXI)



(XXXII)

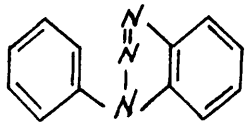


(XXXIII)

on carbazole. The diethyl ester of (XXXI) was obtained both by direct esterification of the acid as described by Dunlop and Tucker and by treatment of 3:6-di-trichloracetylcarbazole with sodium in ethyl alcohol. This method, contrary to the general finding of Houben and Fischer[12], was preferable to the use of potassium acetate in alcohol.

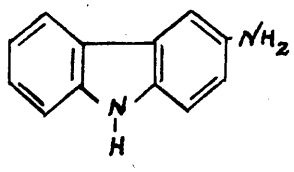
Latterly we found it simpler and equally satisfactory to nitrate 3:6-di-trichloracetylcarbazole (XXXII) and hydrolyse the product (XXXIII) to 1-nitrocarbazole-3:6-dicarboxylic acid (XXX) with dilute sodium hydroxide solution.

We have also managed to prepare 1-nitrocarbazole, in small yield, by a Graebe-Ullmann synthesis. In the synthesis of carbazole by this method[13] the last stage

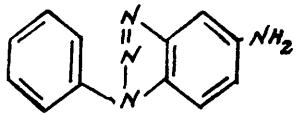


(XXXIV)

is completed by heating 1-phenyl-1:2:3-benzotriazole (XXXIV). When either of the benzene rings of the compound (XXXIV) contains a saturated substituent, e.g., amino or alkyl, conversion to the corresponding carbazole derivative is readily accomplished. Thus Ullmann[14]



(XXXV)



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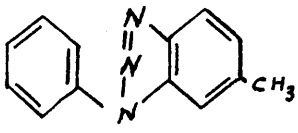
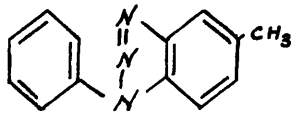
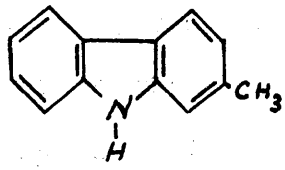


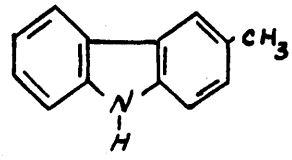
(XXXVII)



(XXXVIII)

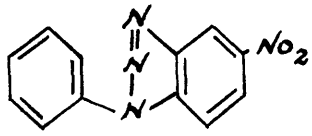


(XXXXIX)

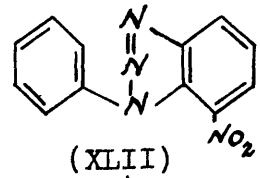


(XL)

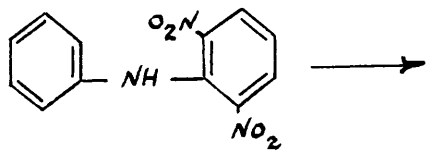
obtained 3-aminocarbazole (XXXV) by pyrogenesis of 1-phenyl-5-amino-1:2:3-benzotriazole (XXXVI) and 1-phenyl-6-methyl-1:2:3-benzotriazole (XXXVII) and 1-phenyl-5-methyl-1:2:3-benzotriazole (XXXVIII) have been respectively converted to 2-methylcarbazole (XXXIX)[15] and 3-methylcarbazole (XL)[16]. Attempts to prepare nitro derivatives of carbazole by this method, however, have, hitherto, been unsuccessful. Delétra and Ullmann[17] failed to convert 1-phenyl-5-nitro-1:2:3-benzotriazole (XLI) into 3-nitrocarbazole (XXVIII) and Borsche and Rantscheff[18] could not obtain 1-nitrocarbazole (XIX) from 1-phenyl-7-nitro-



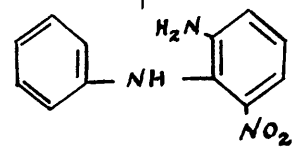
(XLI)



(XLII)



(XLIII)

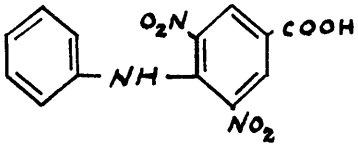


(XLIV)

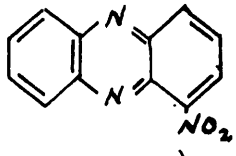
1:2:3-benzotriazole (XLII). The last compound was synthesised, as shown above, from 2:6-dinitrodiphenylamine (XLIII), which arose on treatment of 2:6-dinitrochlorobenzene with aniline.

In view of the recent syntheses of 3-nitro-, 3-cyano- and 3-acetylcarbazole by the Graebe-Ullmann method[19], it was considered worth while to make another attempt to prepare 1-nitrocarbazole by this procedure.

2:6-Dinitrodiphenylamine (XLIII) was obtained in small yield by decarboxylation, by boiling with copper in



(XLV)



(XLVI)

quinoline, of 2:6-dinitrodiphenylamine-4-carboxylic acid (XLV)*, which arose on condensation of 3:5-dinitro-4-chlorobenzoic acid with aniline. A by-product in the decarboxylation reaction may possibly be 1-nitrophenazine (XLVI). The conversion of (XLIII) to the triazole (XLII) was accomplished by methods somewhat similar to those

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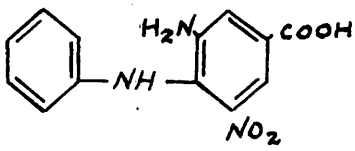
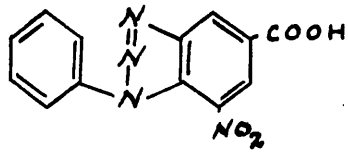
*This method was employed since a supply of 2:6-dinitrochlorobenzene was not at first available (cf. Borsche and Rantscheff, Ann., 1911, 379, 157, footnote 3). Latterly 2:6-dinitrodiphenylamine was prepared by condensing aniline with 2:6-dinitrochlorobenzene, synthesised by Dr. Tucker (unpublished work).

used by Borsche and Rantscheff[18], who, however, gave but the scantiest details. 1-Phenyl-7-nitro-1:2:3-benzotriazole (XLII) can be sublimed unchanged but gentle boiling in presence of copper-bronze converted it, in 18% yield, to 1-nitrocarbazole (XIX).

Attempts to convert 1-phenyl-7-nitro-1:2:3-benzotriazole-5-carboxylic acid (XLVIII) to 1-nitrocarbazole

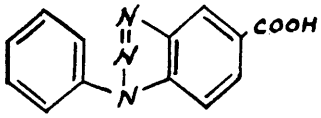


(XLVII)

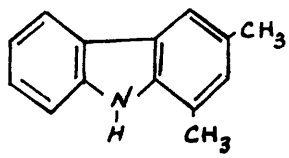


(XLVIII)

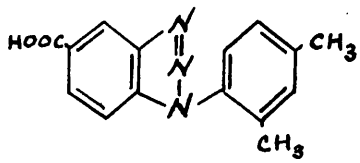
were unsuccessful although Ullmann[20] prepared carbazole from 1-phenyl-1:2:3-benzotriazole-5-carboxylic acid (XLIX) and 1:3-dimethylcarbazole (L) from 1-(2':4'-dimethylphenyl)-1:2:3-benzotriazole-5-carboxylic acid (LI).



(XLIX)



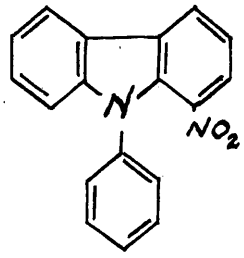
(L)



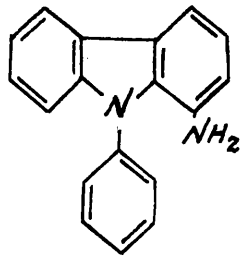
(LI)

The triazole (XLVIII) was readily obtained from the amine (XLVII) which arose by partial reduction of 2:6-dinitrodiphenylamine-4-carboxylic acid (XLV).

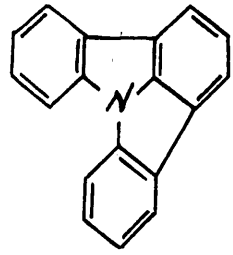
1-Nitrocarbazole (XIX) was condensed with iodobenzene (⟶ XX) in presence of potassium carbonate and copper bronze: a method adopted by Dunlop and Tucker[4]



(XX)

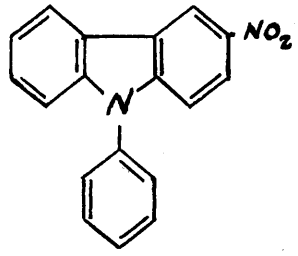


(XXI)



(XIV)

for the preparation of several 9-substituted derivatives of carbazole. Reduction of (XX) by means of sodium sulphide gave 1-amino-9-phenylcarbazole (XXI) which, by diazotisation with an aqueous solution of sodium nitrite in a mixture of glacial acetic and concentrated sulphuric acids, followed by boiling, gave 1:9-phenylenecarbazole (XIV).



(LII)

3-Nitro-9-phenylcarbazole (LII) was prepared, for comparison with (XX), by condensing iodobenzene with 3-nitrocarbazole.

EXPERIMENTAL.

Cyclohexanone diphenylenehydrazone.

A solution of 9-aminocarbazole (5 g.) in alcohol (50 c.c.) containing cyclohexanone (2.7 g.) was boiled for 2½ hours. On cooling a theoretical yield of the hydrazone crystallised in colourless needles m.p. 96°.

Attempted preparations of 1:9-(3':4':5':6'-tetrahydrophenylene)carbazole.

1. A mixture of the above hydrazone (1 g.), glacial acetic acid (8 c.c.) and concentrated hydrochloric acid (1 c.c.) was boiled for 10 minutes before being poured into a large volume of water. From the tarry green solid which was precipitated only carbazole could be isolated.

2. The hydrazone (1 g.), glacial acetic acid (12 c.c.), concentrated sulphuric acid (2 c.c.) and water (5 c.c.) were boiled together for 25 minutes. On dilution of the mixture with water a sticky solid, which consisted mainly of carbazole, was precipitated.

3. A solution of the hydrazone (3.5 g.) in glacial acetic acid (45 c.c.) was boiled under reflux. After 6 hours a colourless material was slowly precipitated

and boiling was continued for a further 6 hours. The insoluble material was removed and crystallised from alcohol in colourless needles, (1.5 g.), melting at 247°.

It was identified as 9-acetylaminocarbazole since the melting point was not depressed on admixing with an authentic specimen of 9-acetylaminocarbazole, m.p. 247° (Blom, J.pr.Chem., 1916, 94, 79).

4. A solution of the hydrazone (1 g.) in a large volume of 20% sulphuric acid was heated on the water bath for a few minutes. An almost theoretical quantity of carbazole was produced.

5. A solution of the hydrazone (0.5 g.) in absolute alcohol (15 c.c.) was saturated with dry hydrogen chloride, and boiled for 45 minutes. The alcohol was removed in vacuo and the residue treated with a mixture of ether and water. From the material obtained by evaporation of the ether extract only carbazole could be isolated.

1:9-(3':4':5':6'-tetrahydrophenylene)carbazole.

A solution of cyclohexanone diphenylenehydrazone (4 g.) in tetralin (60 c.c.), previously distilled over sodium, was added slowly to pure tetralin (20 c.c.) at

165° saturated with dry hydrogen chloride. The solution turned dark brown in colour and an unidentified solid (1 g.), which separated, was removed. The tetralin was removed in steam and the residue, solidified by scratching under ligroin (b.p. 40-60°), was dissolved in warm carbon tetrachloride. After removal of some carbazole, which separated on cooling, the carbon tetrachloride was allowed to evaporate. The tetrahydrophenylenecarbazole obtained crystallised from acetone and then from methyl alcohol in colourless needles m.p. 100-101°. (Found: C, 87.96; H, 6.18; N, 5.65. $C_{18}H_{15}N$ requires C, 88.16; H, 6.12; N, 5.71%).

The 1:3:5-trinitrobenzene compound, prepared in alcoholic solution, crystallised from alcohol in orange-red needles m.p. 164-166°. (Found: C, 62.80; H, 4.09; N, 12.28. $C_{18}H_{15}N.C_6H_3O_6N_3$ requires C, 62.88; H, 3.93; N, 12.23%).

The picrate was prepared in alcoholic solution, and crystallised from alcohol in bronze coloured needles m.p. 159-160°. (Found: C, 60.62; H, 3.82; N, 11.97. $C_{18}H_{15}N.C_6H_3O_7N_3$ requires C, 60.76; H, 3.80; N, 11.81%).

1:9-Phenylenecarbazole.

A solution of tetrahydrophenylenecarbazole (0.1 g.)

in quinoline (2 c.c.) was boiled with sulphur (0.026 g.) till the liberation of hydrogen sulphide ceased. Ether was added to the cold solution and the quinoline was removed by shaking several times with dilute hydrochloric acid. The solid obtained from the ether was sublimed at 260-270°/12 m.m., and crystallised from methyl alcohol in silky needles m.p. 135°. The melting point was not depressed on admixture with an authentic specimen of 1:9-phenylenecarbazole prepared by Dunlop and Tucker.

The 1:3:5-trinitrobenzene complex, prepared in alcohol, crystallised therefrom in yellow needles m.p. 192-193°.

Ethyl carbazole-3:6-dicarboxylate.

3:6-Di-trichloracetylcarbazole (2 g.) was added to a solution of sodium ethoxide (from 0.1 g. of sodium) in absolute alcohol (10 c.c.) and the mixture occasionally shaken over a period of 5 hours (a slightly better yield was obtained on standing for 2-3 days). Dilute ammonia solution was added and the precipitate was removed by filtration. On acidification of the filtrate a small quantity of carbazole-3:6-dicarboxylic acid (0.15 g.) was obtained. The dried precipitate was extracted with toluene (charcoal) from which solution pale cream prisms of ethyl carbazole-3:6-dicarboxylate (0.9 g.; yield 67%),

m.p. 206°, separated on cooling.

Ethyl 1-nitrocarbazole-3:6-dicarboxylate.

A mixture of concentrated nitric acid (15 c.c.) and glacial acetic acid (20 c.c.) was added, all at once, to a solution of ethyl carbazole-3:6-dicarboxylate (7 g.) in glacial acetic acid (100 c.c.). After standing for 15 minutes the mixture was heated to the boiling point and allowed to cool. The crude ethyl 1-nitrocarbazole-3:6-dicarboxylate, which separated, was washed with dilute ammonia solution, dried, and recrystallised from acetic anhydride, in yellow micro-crystals, which softened at 257° and melted at 261°. (Found: C, 60.9; H, 4.4; N, 7.9. $C_{18}H_{16}O_6N_2$ requires C, 60.7; H, 4.5; N, 7.9%).

The acetic acid liquor on dilution with water gave a material (probably ethyl 1-nitro-9-nitrosocarbazole-3:6-dicarboxylate) which on boiling with acetic anhydride evolved nitrous fumes and on cooling gave a further crop of ethyl 1-nitrocarbazole-3:6-dicarboxylate. The total yield was 7.1 g. (90%).

1-Nitro-3:6-di-trichloracetylcarbazole.

Concentrated nitric acid (21 c.c.) was added to a

hot solution of 3:6-di-trichloracetylcarbazole (7 g.) in glacial acetic acid (70 c.c.) and the temperature of the mixture raised carefully to the boiling point. When the vigorous reaction which set in had subsided, the mixture was boiled for 1 minute and left to crystallise. The nearly pure product (6.5 g.; yield 83%) which separated crystallised from acetic anhydride and then from acetic acid in bright yellow needles m.p. 247-249°. (Found: N, 5.4; Cl, 42.5. $C_{16}H_6O_4N_2Cl_6$ requires N, 5.6; Cl, 42.35%).

1-Nitrocarbazole-3:6-dicarboxylic acid.

1. From ethyl 1-nitrocarbazole-3:6-dicarboxylate.

Saponification of the ester was effected in theoretical yield by boiling for 5 minutes with aqueous-alcoholic potassium hydroxide and then acidifying with hot acetic acid. For analysis a specimen was crystallised from acetic anhydride in yellow micro-crystals which remained unmelted at 300°. (Found: C, 55.9; H, 2.8; N, 9.2. $C_{14}H_8O_6N_2$ requires C, 56.0; H, 2.7; N, 9.3%).

2. From 1-nitro-3:6-di-trichloracetylcarbazole.

1-Nitro-3:6-di-trichloracetylcarbazole was heated

with excess of dilute sodium hydroxide solution. Chloroform was driven off, and the deep scarlet solution treated with excess of hot glacial acetic acid. The 1-nitrocarbazole-3:6-dicarboxylic acid which precipitated was sufficiently pure for decarboxylation as described below.

1-Nitrocarbazole.

A solution of 1-nitrocarbazole-3:6-dicarboxylic acid (1 g.) in pure quinoline (5 c.c.) containing a small amount of copper bronze, was boiled for 2 hours. The solvent was removed in steam and the black residue was washed with hot dilute hydrochloric acid and with water, dried and extracted with boiling benzene (charcoal, 1 hour). The concentrated benzene solution deposited on cooling bronze-yellow needles of 1-nitrocarbazole (0.24 g.; yield 34%), m.p. 187°, identical with an authentic specimen.

Charring occurred when 1-nitrocarbazole-3:6-dicarboxylic acid was heated alone.

2:6-Dinitrodiphenylamine-4-carboxylic acid.

A boiling alcoholic solution of 4-chloro-3:5-dinitrobenzoic acid (20 g.) was treated with redistilled

aniline (15 g.). On cooling yellow needles of 2:6-dinitro-diphenylamine-4-carboxylic acid, m.p. 239°, separated (23 g.; yield 96%). Recrystallisation from alcohol did not raise the melting point. (Found: C, 51.21; H, 3.05. Calculated for $C_{13}H_9O_6N_3$: C, 51.49; H, 2.97%).

2-Amino-6-nitrodiphenylamine-4-carboxylic acid.

Sodium sulphide ($Na_2S.9H_2O$; 7.5 g.), sulphur (2 g.) and alcohol (1 c.c.) were warmed to give a clear brown solution which was added to a solution of 2:6-dinitrodiphenylamine-4-carboxylic acid (9.5 g.) in a mixture of alcohol (300 c.c.) and water (200 c.c.) containing sodium hydroxide (1.26 g.). After 3 hours' boiling, the filtered solution was concentrated to 400 c.c., again filtered, and treated with hydrochloric acid until turbid. On cooling 2-amino-6-nitrodiphenylamine-4-carboxylic acid separated. (5.7 g.; yield 67%). Crystallisation from methyl alcohol gave dark red needles melting at 235°. (Found: C, 56.9; H, 4.2; N, 15.5. $C_{13}H_{11}O_4N_3$ requires C, 57.1; H, 4.0; N, 15.4%).

In the absence of sodium hydroxide and water, used above, the yield was reduced to 37%.

1-Phenyl-7-nitrobenztriazole-5-carboxylic acid.

Sodium nitrite (2.6 g.), dissolved in a small quantity of water, was added in the cold to a solution of 2-amino-6-nitrodiphenylamine-4-carboxylic acid (1 g.) in glacial acetic acid (30 c.c.). The mixture was boiled for 10 minutes and on cooling yellow crystals formed. Recrystallisation from glacial acetic acid gave 1-phenyl-7-nitrobenztriazole-5-carboxylic acid (0.7 g.) melting at 271°. (Found: N, 19.5. $C_{13}H_8O_4N_4$ requires N, 19.7%).

The following unsuccessful attempts were made to convert 1-phenyl-7-nitrobenztriazole-5-carboxylic acid to 1-nitrocarbazole:-

1).	Heating carefully to 290°.	Triazole sublimed unchanged.
2).	Heating with copper bronze.	Violent explosion and complete decomposition.
3).	Boiling solution in quinoline with copper chromite catalyst.	Complete charring.
4).	Boiling solution in quinoline with copper bronze.	Complete charring.
5).	Heating suspension in acetic acid-sulphuric acid (50-50).	Triazole unchanged.
6).	Heating suspension in syrupy phosphoric acid.	Triazole unchanged.

7).	Heating to 300° for 90 minutes in paraffin.	Complete decomposition.

2:6-Dinitrodiphenylamine.

2:6-Dinitrodiphenylamine-4-carboxylic acid (1 g.) was decarboxylated by boiling for 15 minutes in quinoline, in presence of copper bronze. The solution was poured into excess of dilute hydrochloric acid, and the insoluble material extracted with dilute ammonia to remove any unchanged acid, dried, and extracted with hot benzene (charcoal, 1 hour). The scarlet residue obtained on evaporation of the benzene was dissolved in glacial acetic acid and on dilution with a drop of water gave dark red crystals of 1-nitrophenazine (?), m.p. 192-195°. (Found: C, 63.7; H, 3.2; N, 18.5. $C_{12}H_7O_2N_3$ requires C, 64.0; H, 3.1; N, 18.7%). The acetic acid filtrate on scratching deposited scarlet crystals of 2:6-dinitrodiphenylamine (0.1 g.; yield 11%) melting at 107-108°.

2-Amino-6-nitrodiphenylamine. (Cf. Borsche and Rantscheff, Ann., 1911, 379, 168, who gave no quantities).

A mixture of the above dinitro compound (1 g.), alcohol (10 c.c.) and concentrated ammonia solution (1.5 c.c. was warmed and hydrogen sulphide passed until the scarlet

crystals dissolved. The solution was boiled, filtered from sulphur, and excess of dilute hydrochloric acid was added. The black precipitate, on crystallisation from alcohol, gave dark red crystals of 2-amino-6-nitrodiphenylamine, m.p. 101°.

1-Phenyl-7-nitrobenztriazole.

Diazotisation of the above amine was accomplished by treating a glacial acetic acid solution with excess of sodium nitrite. 1-Phenyl-7-nitrobenztriazole cryatallised from acetic acid in prisms m.p. 152°.

1-Nitrocarbazole.

The above triazole (2.5 g.) was gently boiled in presence of copper bronze (0.5 g.) until the nitrogen evolution had ceased. The black residue was extracted with benzene (charcoal) and from the concentrated benzene solution 1-nitrocarbazole (0.39 g.; yield 18%) m.p. 187° separated on standing.

The triazole distilled unchanged when heated in absence of copper bronze.

1-Nitro-9-phenylcarbazole.

A mixture of 1-nitrocarbazole (1.2 g.), iodobenzene (6 c.c.), anhydrous potassium carbonate (1.2 g.) and

copper bronze (0.01 g.) was boiled on a metal bath for 6 hours. More potassium carbonate (0.5 g.) was added (there was effervescence and the colour of the liquid changed from yellow to red) and the heating was continued for a further 2 hours. The excess iodobenzene was removed by distillation and the residue was treated with dilute hydrochloric acid, washed with water and extracted with boiling ligroin (80-100°). From the filtered extract nearly pure product separated on cooling. Recrystallisation from methyl alcohol or from a mixture of benzene and ligroin (80-100°) gave stout yellow prisms of 1-nitro-9-phenylcarbazole (1.1 g.; yield 69%) melting at 130-132°. (Found: C, 75.0; H, 4.3; N, 9.9. $C_{18}H_{12}O_2N_2$ requires C, 75.0; H, 4.2; N, 9.7%).

1-Amino-9-phenylcarbazole.

A mixture of 1-nitro-9-phenylcarbazole (0.8 g.) and sodium sulphide ($Na_2S.9H_2O$; 2 g.) in alcohol (10 c.c.) was boiled for 3 hours. Water was added to the boiling solution until turbidity was produced. The material which separated on cooling was extracted with ligroin (60-80°) and the product was crystallised from this solvent and then from alcohol (plus a drop of water). The

pale brown laminae of 1-amino-9-phenylcarbazole (0.33 g.; yield 46%) obtained melted at 96-98°. (Found: C, 83.9; H, 5.6; N, 10.7. $C_{18}H_{14}N_2$ requires C, 83.7; H, 5.4; N, 10.8%).

1:9-Phenylenecarbazole.

To a solution of 1-amino-9-phenylcarbazole (0.33 g.) in glacial acetic acid (3.5 c.c.) concentrated sulphuric acid (0.7 c.c.) was added followed by a solution of sodium nitrite (0.09 g.) in water (2 c.c.). The colour of the paste changed from brown to red. After 15 minutes the mixture was gently warmed until effervescence ceased and finally boiled for 15 minutes. The material which separated on cooling was washed with dilute acid (1:1), then with water, dried and extracted with alcohol. The product (0.25 g.) obtained by concentration of the extract was sublimed in vacuum and crystallised from a mixture of methyl alcohol and acetone (2:1). The characteristic long colourless needles of 1:9-phenylene-carbazole (0.11 g.; yield 36%) melted at 135-137° alone or mixed with a specimen synthesised by Dunlop and Tucker.

3-Nitro-9-phenylcarbazole.

A mixture of 3-nitrocarbazole (3 g.), iodobenzene (10 c.c.), anhydrous potassium carbonate (3 g.) and copper bronze (0.03 g.) was boiled for 8 hours. The excess iodobenzene was distilled off and the residue was treated with dilute hydrochloric acid and then extracted with hot benzene. The yellow prisms which separated on cooling were recrystallised from a mixture of benzene and methyl alcohol (2:1) giving yellow rosettes of 3-nitro-9-phenylcarbazole (1.8 g.; yield 44%) m.p. 140-142°. (Found: C, 75.1; H, 4.2; N, 9.7. $C_{18}H_{12}O_2N_2$ requires C, 75.0; H, 4.2; N, 9.7%).

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I N D E X.

Part II.