CCCCLIV.—*Polycyclic Aromatic Hydrocarbons. Part VIII. The Chemistry of* 1 : 2 : 5 : 6-*Dibenzanthracene.*

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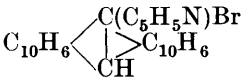
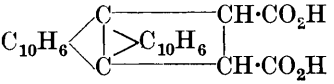
It seemed possible that the cancer-producing activity of 1 : 2 : 5 : 6-dibenzanthracene is associated with its chemical activity, and in attempting to correlate these two factors the *meso*-ring reactivity of this hydrocarbon was investigated for comparison with the well-known reactivity of anthracene.

There was evidence that dibenzanthracene reacted sluggishly with bromine to form an unstable additive compound. With pyridine dibromide, a reagent which gives a qualitative means of distinguishing between different degrees of *meso*-reactivity (Cook, J., 1926, 2162), there was formed an unstable dipyridinium dibromide which lost pyridine hydrobromide under the influence of cold aqueous ammonia and passed into 1 : 2 : 5 : 6-*dibenzanthranyl*-9-*pyridinium bromide* (I). Dibenzanthracene was converted by nitric acid in cold acetic acid into 9-*nitro*-1 : 2 : 5 : 6-*dibenzanthracene*; there was no suggestion of the formation of an additive compound, although anthracene reacts additively under similar conditions (Meisenheimer and Connerade, *Annalen*, 1904, **330**, 133).

The interesting addition of maleic anhydride to anthracene and its derivatives recently observed by Diels and Alder (*Annalen*, 1931, **486**, 191) and by Clar (*Ber.*, 1931, **64**, 2194) provided a further test of *meso*-additive power. 1 : 2 : 5 : 6-Dibenzanthracene reacted with maleic anhydride, but with much greater reluctance than anthracene; to facilitate separation from unattacked hydrocarbon, the additive product was isolated in the form of the *dicarboxylic acid* (II).



(I.)



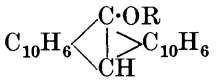
(II.)

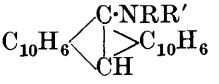
It was thus apparent that the chemical reactivity of 1 : 2 : 5 : 6-dibenzanthracene is of the same degree as that of anthracene, but that the *angular* structure of the molecule tends to stabilise the aromatic state of the *meso*-ring. This contrasts with the influence of *linear* condensation in the anthracene molecule, since in the case of 2 : 3-benzanthracene the dihydro-structure is more stable (Fieser, *J. Amer. Chem. Soc.*, 1931, **53**, 2329), while 2 : 3 : 6 : 7-dibenzanthracene appears to exist only as a deep blue bivalent radical (Clar and John, *Ber.*, 1930, **63**, 2967).

The fact that 1 : 2 : 5 : 6-dibenzanthraquinone and 1 : 2-benzanthraquinone and its derivatives are very resistant to reduction by zinc dust and alkali, whereas the simpler anthraquinone derivatives are usually reduced to the corresponding anthracenes with great facility, also supports this view of the opposing influences of *angular* and *linear Bz* rings; for the initial reduction to the benz-(or dibenz-)anthraquinol takes place easily, the obstruction occurring in the subsequent addition of hydrogen to the *meso*-carbon atoms. With 2 : 3-benzanthraquinone the reverse is true; the difficult initial reduction of the quinone is followed by ready reduction of the benzanthraquinol (Fieser, *loc. cit.*).

The physiological properties of compounds are usually considerably modified by the presence of amino- and hydroxy-groups in the molecule, and it seemed of interest to prepare derivatives of 1 : 2 : 5 : 6-dibenzanthracene containing such groups in order to study their influence on the carcinogenic activity of this hydrocarbon. Reduction of 1 : 2 : 5 : 6-dibenzanthraquinone with tin and hydrochloric acid in acetic acid solution led to a very sparingly soluble quinhydrone-like compound which was not further attacked. By reduction with aluminium powder and concentrated sulphuric acid, 1 : 2 : 5 : 6-dibenzanthranol was formed; it was not obtained pure on account of its susceptibility to atmospheric oxidation, but was converted by acetic anhydride into 9-*acetoxy*-1 : 2 : 5 : 6-*di*-

benzanthracene (III; R = $CO{\cdot}CH_3$) and by methyl sulphate into 9-*methoxy*-1 : 2 : 5 : 6-*dibenzanthracene* (III; R = CH_3).

(III.) 

 (IV.)

It has been shown that the facile hydrolysis of 9-anthranyl ethers is due to primary addition to the *meso*-carbon atoms (Barnett, Cook, and Matthews, *Rec. trav. chim.*, 1925, **44**, 732), so that the stability of 9-methoxy-1 : 2 : 5 : 6-dibenzanthracene under conditions which suffice for the complete hydrolysis of the simpler ethers of the anthracene series is further evidence of the suppression of *meso*-additive power in the 1 : 2 : 5 : 6-dibenzanthracene series.

9-Nitro-1 : 2 : 5 : 6-dibenzanthracene was reduced to the 9-*amino*-compound (IV; R = R′ = H) by brief boiling with phenylhydrazine, although reduction with stannous chloride in glacial acetic acid was ineffectual. The constitution of the amine, and hence of the nitro-compound, was established by oxidation by chromic acid to 1 : 2 : 5 : 6-dibenzanthraquinone; the amine gave 9 - *diacetylamino* - 1 : 2 : 5 : 6 - *dibenzanthracene* (IV; R = R′ = $CO{\cdot}CH_3$), with boiling acetic anhydride, and 9-n-*butyrylamido*-1 : 2 : 5 : 6-*dibenzanthracene* (IV; R = H; R′ = $CO{\cdot}C_3H_7$) with *n*-butyryl chloride in pyridine, whereas heating with succinic anhydride yielded N-1 : 2 : 5 : 6-*dibenzanthranyl succinimide* (IV; RR′ = $C_4H_4O_2$).

Investigation of the cancer-producing properties of 1 : 2 : 5 : 6-dibenzanthracene has led to the development of a new method of producing connective tissue tumours (Burrows, Hieger, and Kennaway, private communication) and it is anticipated that the discovery of a water-soluble substance having carcinogenic activity will be of service in the experimental study of cancer. As a preliminary step, the sulphonation of 1 : 2 : 5 : 6-dibenzanthracene has been attempted. Treatment with concentrated sulphuric acid at 50—60° gave a product which seemed to consist essentially of disulphonic acids, as shown by the barium content of the easily soluble barium salts. Both the barium and sodium salts had poor power of crystallisation and no pure compound was isolated.

EXPERIMENTAL.

Action of Bromine on 1 : 2 : 5 : 6-*Dibenzanthracene.*—A suspension of the finely powdered hydrocarbon (1 mol.) in carbon disulphide slowly reacted with bromine (1 mol.). After 18 hours at room temperature, the product was collected and dried over solid potassium hydroxide. It was evidently a mixture of dibenzanthracene

with a bromine additive compound; boiling pyridine decomposed the chief constituent, so that a little dibenzanthracene crystallised on cooling; boiling xylene liberated hydrogen bromide and gave a mixture from which no pure substance could be isolated.

When 2 mols. of bromine were employed, much was unabsorbed and some substitution occurred, since crystallisation of the product from boiling pyridine gave a product of very indefinite melting point.

1 : 2 : 5 : 6-*Dibenzanthranyl*-9-*pyridinium Bromide* (I).—A cold suspension of finely powdered 1 : 2 : 5 : 6-dibenzanthracene (2·8 g.) in pyridine (10 c.c.) was treated with a solution of bromine (0·5 c.c.; 1 mol.) in pyridine (4 c.c.). After 4 hours at room temperature, the product was collected, washed with pyridine and ether, and dried. The substance was extracted with a large volume of water at 50° (it was decomposed at higher temperatures), and the filtered solution treated with hydrobromic acid. The colourless crystals which separated had the properties of a dihydroanthraquinyl dipyridinium salt (Barnett and Cook, J., 1921, **119**, 901). A solution of this salt (0·6 g.) in cold water (200 c.c.) was treated with 2*N*-aqueous ammonia (10 c.c.), and after ½ hour the yellow solution was acidified with hydrobromic acid. The monopyridinium bromide separated as a curd which was coagulated by boiling; the product was collected, dried, and recrystallised from alcohol with the addition of ether. 1 : 2 : 5 : 6-*Dibenzanthranyl*-9-*pyridinium bromide* (I) formed a yellowish crystalline powder, sparingly soluble in water, with no definite melting point (Found: C, 73·9; H, 4·3. $C_{27}H_{18}NBr$ requires C, 74·3; H, 4·1%). Addition of aqueous sodium hydroxide to a cold solution of the bromide gave an orange precipitate which became red on boiling.

9-*Nitro*-1 : 2 : 5 : 6-*dibenzanthracene*.—Nitric acid (*d* 1·5; 2 c.c.) was added to a suspension of finely powdered 1 : 2 : 5 : 6-dibenzanthracene (5·6 g.) in glacial acetic acid (50 c.c.). After 18 hours at room temperature, the crude nitro-compound was collected, and washed with acetic acid. The product had none of the properties of an additive compound, and was purified by recrystallisation from xylene. 9-*Nitro*-1 : 2 : 5 : 6-*dibenzanthracene* formed orange-yellow needles, m. p. 217—218° (Found: C, 81·6; H, 4·2. $C_{22}H_{13}O_2N$ requires C, 81·7; H, 4·0%).

9-*Amino*-1 : 2 : 5 : 6-*dibenzanthracene* (IV; R = R′ = H).—A solution of the nitro-compound (1·5 g.) in phenylhydrazine (10 c.c.) was boiled for 20 minutes, cooled somewhat, and diluted with alcohol. The product was recrystallised from pyridine and washed with alcohol; it then formed yellow leaflets, m. p. 268—269° (Found: C, 90·0; H, 5·4. $C_{22}H_{15}N$ requires C, 90·1; H, 5·1%). Oxidation

of this *amine* with chromic acid in glacial acetic acid gave 1 : 2 : 5 : 6-dibenzanthraquinone, identified by direct comparison with a sample prepared by oxidation of the hydrocarbon.

9-*Diacetylamino*-1 : 2 : 5 : 6-*dibenzanthracene* (IV; R = R′ = $CO{\cdot}CH_3$).—A suspension of the crude amine (from 1·3 g. of the nitro-compound) in acetic anhydride (35 c.c.) was boiled for ¼ hour. The crystals which separated on cooling were extracted with boiling xylene. There remained undissolved a small amount of a yellow monoacetyl compound, m. p. 305—307° (decomp.), also obtained by acetylation of the amine with acetyl chloride in pyridine; this product could not be obtained analytically pure. The xylene extract gave 9-*diacetylamino*-1 : 2 : 5 : 6-*dibenzanthracene*, which separated from glacial acetic acid as very pale yellow needles, m. p. 215—216·5° (Found: C, 82·4; H, 5·3. $C_{26}H_{19}O_2N$ requires C, 82·8; H, 5·0%).

9-n-*Butyrylamido*-1 : 2 : 5 : 6-*dibenzanthracene* (IV; R = H; R′ = $CO{\cdot}C_3H_7$) was obtained by treatment of the amine (2 g.) with *n*-butyryl chloride (2 c.c.) in pyridine (20 c.c.). It crystallised from pyridine as colourless leaflets, m. p. 300—302° (Found: C, 85·8; H, 5·8. $C_{26}H_{21}ON$ requires C, 86·0; H, 5·8%).

N-1 : 2 : 5 : 6-*Dibenzanthranylsuccinimide* (IV; RR′ = $C_4H_4O_2$).—A mixture of the amine (2 g.) and succinic anhydride (10 g.) was heated for an hour at 215°. The product was extracted with boiling water, and the residue crystallised from pyridine–alcohol and glacial acetic acid (Found: C, 83·0; H, 4·6. $C_{26}H_{17}O_2N$ requires C, 83·2; H, 4·5%). The *succinimide* formed colourless leaflets, m. p. 299—300°, insoluble in alkali.

1 : 2 : 5 : 6-*Dibenzanthracene*-9 : 10-endo-αβ-*succinic Acid* (II).—A mixture of 1 : 2 : 5 : 6-dibenzanthracene (2·8 g.) and maleic anhydride (1·3 g.) was heated at 250—260° for 20 minutes. After cooling, the powdered mass was extracted with boiling dilute sodium hydroxide solution. The insoluble residue (1·8 g.) consisted of unchanged dibenzanthracene, and the proportion was not materially altered by increasing the amount of maleic anhydride or by prolonging the heating for an hour. The recovered hydrocarbon was quite free from the yellow impurity present in the original substance. The alkaline extract from the above experiment was acidified, and the precipitate collected, dried, and recrystallised from glacial acetic acid. The *dicarboxylic acid* (II) formed a colourless crystalline powder, m. p. 230° (Found: C, 79·2; H, 4·6. $C_{26}H_{18}O_4$ requires C, 79·2; H, 4·6%).

The sparingly soluble *disodium* salt of the above acid separated from hot water as a colourless crystalline powder (Found: Na, 9·6. $C_{26}H_{16}O_4Na_2,2H_2O$ requires Na 9·7%).

When 1 : 2 : 5 : 6-dibenzanthracene (2 parts) was treated with maleic anhydride (1 part) in boiling xylene for 5 hours, most of the hydrocarbon was recovered unchanged. Under similar conditions anthracene condenses completely in about 10 minutes, and 2 : 3-benzanthracene condenses very rapidly (Clar, *loc. cit.*).

Reduction of 1 : 2 : 5 : 6-*Dibenzanthraquinone.*—Fine aluminium powder (0·5 g.) was added gradually, with constant agitation, to a solution of the quinone (2 g.) in concentrated sulphuric acid (20 c.c.). The colour of the solution changed from purple to orange-red. After 2 hours, the solution was poured into ice-water, and the precipitate collected, dried in a vacuum desiccator, and dissolved in a mixture of pyridine (15 c.c.) and acetic anhydride (10 c.c.). The solution, filtered from aluminium, was heated on the water-bath for an hour, cooled, and diluted with water, and the crystalline product extracted with boiling alkaline sodium hydrosulphite to remove a trace of quinone. The dried residue was recrystallised from benzene (Found : C, 85·7; H, 4·7. $C_{24}H_{16}O_2$ requires C, 85·7; H, 4·8%). 9-*Acetoxy*-1 : 2 : 5 : 6-*dibenzanthracene* (III; R = $CO{\cdot}CH_3$) formed colourless microscopic needles, m. p. 235°, which had a violet fluorescence in benzene solution, and gave an orange solution in concentrated sulphuric acid. This acetate was hydrolysed by boiling alcoholic potassium hydroxide; the dibenzanthranol was precipitated on acidification of the yellow aqueous solution of its potassium salt, but was too readily oxidised to be isolated in the pure state.

When the above preparation was repeated with 15 g. of the quinone, the acetoxy-compound obtained was contaminated with a by-product, very sparingly soluble in benzene. This separated from xylene in colourless silky needles, m. p. 300°, after darkening, and gave an orange-red solution in alcoholic potassium hydroxide. It was evidently the acetate of an oxidation product formed during the very slow filtration of the crude dibenzanthranol.

9-*Methoxy*-1 : 2 : 5 : 6-*dibenzanthracene* (III; R = CH_3).—A suspension of the acetoxy-compound (1·5 g.), m. p. 235°, in boiling alcohol (50 c.c.) was treated alternately with 50% aqueous potassium hydroxide and methyl sulphate until the orange-red colour of the solution was permanently destroyed. The product was extracted with alkaline sodium hydrosulphite to remove a little quinone, and then crystallised from benzene (Found : C, 89·7; H, 5·0. $C_{23}H_{16}O$ requires C, 89·6; H, 5·2%). This *methoxy*-compound formed a colourless crystalline powder, m. p. 178°, and was recovered entirely unchanged after its solution in acetic acid containing hydrochloric acid had been boiled for an hour.

Conclusions.

1. The cancer-producing property of 1 : 2 : 5 : 6-dibenzanthracene is not primarily due to any enhanced chemical activity of the anthracene ring system present in the molecule, although it is still possible that the *meso*-activity is a contributory factor.

2. 1 : 2 : 5 : 6-Dibenzanthracene is endowed with *meso*-additive power similar in nature to that of anthracene, but to a subdued extent.

3. Additional benzene rings, condensed to the anthracene molecule, strengthen the aromatic character of the *meso*-ring in compounds of an *angular* structure, although they weaken it in *linear* compounds.

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