86. *The Synthesis of Growth-inhibitory Polycyclic Compounds. Part II.*

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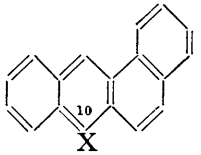
In continuation of previous work a further series of water-soluble compounds derived from the growth-inhibitory carcinogenic hydrocarbons, 10-methyl- and 9 : 10-dimethyl-1 : 2-benzanthracene, has been prepared. A preliminary report of tests for growth-inhibitory properties carried out with nineteen compounds, described in the present communication and in Part I, showed that four of these had definite activity; only one of the active compounds (sodium 1 : 2-benz-10-anthroate) was water-soluble. The introduction of hydroxyl and carboxyl groups is attended by marked loss of growth-inhibitory activity.

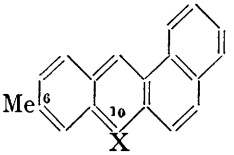
In Part I (J., 1939, 802) we described the synthesis of several derivatives of 10-methyl- and 9 : 10-dimethyl-1 : 2-benzanthracene containing oxygen or nitrogen. This work, forming part of a more comprehensive study of the influence of introduction of water-solubilising groups on the biological properties of polycyclic hydrocarbons, has been extended. A further series of substituents has been introduced into the 10-position of 1 : 2-benzanthracene and on account of the favourable influence of methyl groups at positions 6 and 9 on carcinogenic activity (which is correlated with growth-inhibitory activity), some 6-methyl (II) and 9-methyl (III) derivatives of the 10-substituted benzanthracenes have also been prepared.

Bromination of 1 : 2-benzanthracene led to 10-*bromo*-1 : 2-*benzanthracene* (I; X = Br), which was transformed by cuprous cyanide in phenylacetonitrile into 10-cyano-1 : 2-benzanthracene, a compound obtained by Fieser and Hartwell (*J. Amer. Chem. Soc.*, 1938, **60**, 2558) by dehydration of the corresponding aldoxime of proved orientation.

This nitrile was resistant to catalytic hydrogenation and to chemical reduction, and could not be hydrolysed beyond the stage of 1 : 2-*benz*-10-*anthramide* (I; X = $CO{\cdot}NH_2$). 1 : 2-Benz-10-anthranylmagnesium bromide reacted with ethylene oxide to give 10-β-*hydroxyethyl*-1 : 2-*benzanthracene* (I; X = $CH_2{\cdot}CH_2{\cdot}OH$).



(I.)



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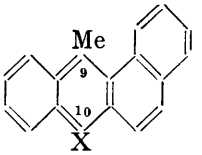

(III.)

The 1 : 2-benz-10-anthraldehyde of Fieser and Hartwell (*loc. cit.*) was oxidised by permanganate in acetone solution to 1 : 2-benz-10-anthroic acid, a substance obtained by Dansi (*Gazzetta*, 1937, **67**, 86) as a product of interaction of 1 : 2-benzanthracene with oxalyl chloride. Ethyl chloroglyoxylate condensed with 1 : 2-benzanthracene, in presence of anhydrous aluminium chloride, to give 1 : 2-*benzanthranyl*-10-*glyoxylic acid* (I; X = $CO{\cdot}CO_2H$), which was reduced by sodium amalgam to *α-hydroxy*-1 : 2-*benzanthranyl*-10-*acetic acid* [I; X = $CH(OH){\cdot}CO_2H$], and by hydriodic acid and red phosphorus to 1 : 2-benzanthranyl-10-acetic acid. The latter compound was prepared by Dansi (*Gazzetta*, 1939, **69**, 195) from benzanthracene and ethyl chloroacetate, and its orientation proved by decarboxylation to 10-methyl-1 : 2-benzanthracene. The same 1 : 2-benzanthranyl-10-acetic acid was also obtained by alkaline hydrolysis of 10-*cyanomethyl*-1 : 2-*benzanthracene* (I; X = $CH_2{\cdot}CN$), which was formed from the 10-chloromethyl compound by the action of potassium cyanide in aqueous acetone or of cuprous cyanide in phenylacetonitrile.

In an attempt to obtain an improved method of preparation of 10-acetyl-1 : 2-benzanthracene, which is probably the *meso*-acetylbenzanthracene isolated from the products of interaction of 1 : 2-benzanthracene and acetic anhydride (Cook and Hewett, J., 1933, 1408), 1 : 2-benz-10-anthraldehyde was treated with an ethereal solution of diazomethane containing methyl alcohol (compare Adamson and Kenner, J., 1939, 181). The product, which was different from the *meso*-acetylbenzanthracene obtained by direct substitution, was oxidised by chromic acid to 1 : 2-benzanthraquinone, and is probably 1 : 2-*benzanthranyl*-10-*acetaldehyde* (I; X = $CH_2{\cdot}CHO$).

Dr. Alexander Haddow has carried out tests for growth-inhibitory action with 10-substituted benzanthracenes with the following substituents: $CH_2{\cdot}OH$, $CH_2{\cdot}OEt$, $CH_2{\cdot}OAc$, CHO, CN, CO_2Na, $CH_2{\cdot}CH_2{\cdot}OH$, $CH_2{\cdot}CO_2Na$, $CO{\cdot}CO_2Na$, $CH(CO_2Na)_2$, $CH_2{\cdot}CH_2{\cdot}CO_2Na$, C_5H_5NCl, $C_5H_{10}N,HCl$; and also with the following disubstituted benzanthracenes: 9 : 10-bishydroxymethyl and the corresponding disodium disuccinate, 9 : 10-bisacetoxymethyl, 10-cyano-9-methyl, 9-methyl-10-aldehydo, 10-cyano-6-methyl. Of these, only 1 : 2-benz-10-anthraldehyde and sodium 1 : 2-benz-10-anthroate produced a characteristic inhibition of growth, of moderate intensity, and a definite inhibitory effect was also produced by 10-cyano-1 : 2-benzanthracene and 10-cyano-6-methyl-1 : 2-benzanthracene.

In tests for carcinogenic activity, carried out by Professor E. L. Kennaway, F.R.S., malignant tumours have been obtained in mice with the following compounds: 10-hydroxymethyl, 10-acetoxymethyl (but not 10-ethoxymethyl), 9 : 10-bishydroxymethyl, and 9 : 10-bisacetoxymethyl-1 : 2-benzanthracenes.

Experimental.

10-*Bromo*-1 : 2-*benzanthracene*.—Bromine (8 g.) was slowly added to a solution of 1 : 2-benzanthracene (11·5 g.) in carbon disulphide (150 c.c.). After being kept overnight, the solution was evaporated and the residue was recrystallised from acetic acid. The resulting 10-bromo-1 : 2-benzanthracene (14·8 g.) was purified through its *picrate*, which formed blood-red flat needles (from acetic acid), m. p. 155·5—156·5° (Found: C, 53·7; H, 2·6. $C_{18}H_{11}Br,C_6H_3O_7N_3$ requires C, 53·7; H, 2·6%). The regenerated 10-*bromo*-1 : 2-*benzanthracene* crystallised from acetic acid in almost colourless needles or plates, m. p. 147·5—148·5° (Found: C, 70·6; H, 3·7. $C_{18}H_{11}Br$ requires C, 70·4; H, 3·6%).

10-Cyano-1 : 2-benzanthracene was obtained when a mixture of the bromo-compound (6·5 g.), cuprous cyanide (6·5 g.), and phenylacetonitrile (15 c.c.) was heated at 190—200° for 6 hours. After the complex had been decomposed with hot hydrochloric acid the nitrile was isolated in 85% yield, and had m. p. 187·5—188·5° (corr.) alone or mixed with a specimen prepared by dehydration of 1 : 2-benzanthracene-10-aldoxime (Fieser and Hartwell, *loc. cit.*). This aldoxime in ethereal solution could not be hydrogenated over a platinum catalyst.

1 : 2-*Benz*-10-*anthramide* (0·5 g.) was obtained when the nitrile (1 g.) was refluxed for 120 hours with 25% methyl-alcoholic potash (50 c.c.). It crystallised from benzene in colourless, microscopic needles, m. p. 218—220° (Found: C, 84·1; H, 5·1. $C_{19}H_{13}ON$ requires C, 84·1; H, 4·8%). The nitrile was recovered unchanged after treatment with sulphuric acid in boiling acetic acid under conditions which Newman and Orchin (*J. Amer. Chem. Soc.*, 1938, **60**, 589) used successfully for the preparation of 10-methyl-1 : 2-benz-7-anthroic acid from its nitrile.

10-Cyano-1 : 2-benzanthracene failed to react with methylmagnesium iodide, and was not reduced by amalgamated zinc and hydrochloric acid in acetic acid solution.

10-β-*Hydroxyethyl*-1 : 2-*benzanthracene* (I; X = CH_2·CH_2·OH).—In order to obtain a Grignard compound of 10-bromo-1 : 2-benzanthracene a solution of ethyl bromide (1·2 g.) in ether (2 c.c.) was added to a boiling mixture of bromobenzanthracene (3·07 g.), magnesium turnings (0·52 g.), anhydrous ether (5 c.c.), and anhydrous benzene (15 c.c.). Boiling was continued for 20 hours, and the solution was cooled in ice and treated with ethylene oxide (1 c.c.). After 5 hours the solvents were distilled, and the residue heated on the water-bath for 1½ hours. The product was decomposed with ice and hydrochloric acid, with addition of ether, separated from insoluble material (0·5 g.), and the product recovered from the ether was recrystallised from benzene. 10-β-*Hydroxyethyl*-1 : 2-*benzanthracene* (0·8 g.) formed almost colourless needles, m. p. 181·5—182·5° (Found: C, 87·9; H, 6·0. $C_{20}H_{16}O$ requires C, 88·2; H, 5·9%).

Oxidation of an ice-cold solution of 1 : 2-benz-10-anthraldehyde (Fieser and Hartwell, *loc. cit.*) (1·5 g.) in pure acetone (200 c.c.) with powdered potassium permanganate (1 g.) was complete in 4 hours. The resulting 1 : 2-benz-10-anthroic acid was purified through its sparingly soluble sodium salt and the free acid (0·5 g.) was recrystallised from dilute acetic acid; it then formed almost colourless, microscopic needles, m. p. 219—220°. This was evidently identical with the acid, m. p. 220°, obtained by Dansi (*loc. cit.*) from benzanthracene and oxalyl chloride.

1 : 2-*Benzanthranyl*-10-*glyoxylic Acid* (I; X = CO·CO_2H).—Powdered anhydrous aluminium chloride (15 g.) was added gradually with ice-cooling to a stirred solution of 1 : 2-benzanthracene (11·5 g.) in nitrobenzene (400 c.c.). After ½ hour a solution of ethyl chloroglyoxylate (Adickes, Brunnert, and Lücker, *J. pr. Chem.*, 1931, **130**, 163) (7 g.) in a little nitrobenzene was added dropwise to the stirred solution. After 4 hours in the ice-bath the deep blue solution was kept overnight at room temperature, decomposed with ice and hydrochloric acid, and the nitrobenzene removed in steam. The residual gum was extracted with boiling dilute sodium hydroxide solution. The filtered solution deposited on cooling the sodium salt of 1 : 2-*benzanthranyl*-10-*glyoxylic acid* (10 g.) which, isolated from its salt and recrystallised from acetic acid and then benzene, formed orange-yellow lustrous plates, m. p. 175—176·5° (decomp.) (Found: C, 80·0; H, 3·7. $C_{20}H_{12}O_3$ requires C, 80·0; H, 4·0%).

A solution of this keto-acid (1 g.) in very dilute sodium hydroxide (400 c.c.) was allowed to react overnight with sodium amalgam. The resulting α-*hydroxy*-1 : 2-*benzanthranyl*-10-*acetic acid* (0·25 g.) crystallised from benzene–ether in microscopic colourless needles, m. p. 187—191° (decomp.) (Found: C, 79·6; H, 5·0. $C_{20}H_{14}O_3$ requires C, 79·4; H, 4·7%). Its sodium salt was readily soluble in water. Reduction of the keto-acid (1·5 g.) to 1 : 2-benzanthranyl-10-acetic acid was effected by 3 hours' boiling with hydriodic acid (*d* 1·7; 10·8 g.) and red phosphorus (0·9 g.) in acetic acid (10 c.c.). The reduced acid, which was contaminated with 1 : 2-benzanthracene, was purified through its sparingly soluble sodium salt, and then crystallised from dilute acetic acid in almost colourless, prismatic needles, m. p. 270—274°, after sintering (Dansi, *loc. cit.*, describes this acid as an almost white powder, m. p. 273°, softening at 250°).

10-*Cyanomethyl*-1 : 2-*benzanthracene*.—A mixture of 10-chloromethyl-1 : 2-benzanthracene (Badger and Cook, *loc. cit.*) (2 g.), cuprous cyanide (2 g.), and phenylacetonitrile (10 c.c.) was heated at 180—190° for 6 hours, and the product was decomposed with concentrated hydrochloric acid in presence of benzene. The benzene was removed by distillation, and after 2 days the phenylacetonitrile solution deposited 10-*cyanomethyl*-1 : 2-*benzanthracene*, which crystallised from benzene in colourless silky needles (0·5 g.), m. p. 177—178° (Found: C, 89·9; H, 5·0. $C_{20}H_{13}N$ requires C, 89·85; H, 4·9%). The same nitrile (0·7 g.) was also obtained when a solution of 10-chloromethyl-1 : 2-benzanthracene (1 g.) and potassium cyanide (1 g.) in acetone (100 c.c.) and water (10 c.c.) was boiled for 4 hours. It was hydrolysed to 1 : 2-benzanthranyl-10-acetic acid by 20 hours' boiling with 15% alcoholic potash.

1 : 2-*Benzanthranyl*-10-*acetaldehyde* (?).—Diazomethane (prepared from 5 c.c. of nitrosomethylurethane) was added to a suspension of 1 : 2-benz-10-anthraldehyde (2 g.) in pure methyl alcohol (50 c.c.) and absolute ether (200 c.c.). After 24 hours a further quantity of diazomethane (from 3 c.c. of nitrosomethylurethane) was added and reaction was allowed to proceed for another 48 hours. Excess of diazomethane was destroyed by addition of acetic acid, the solvents removed, and the resinous residue dissolved in alcohol, from which solution a crystalline compound (0·5 g.), m. p. 146—147°, was obtained. This substance evidently contained the intact ring system of benzanthracene, for it was oxidised to 1 : 2-benzanthraquinone by sodium dichromate in boiling glacial acetic acid. The presence of a carbonyl group was indicated by semicarbazone-formation. The compound was clearly not the *meso*-acetyl-1 : 2-

benzanthracene, m. p. 105°, of Cook and Hewett (*loc. cit.*), which has been found not to react with semicarbazide. The new compound is provisionally regarded as 1 : 2-*benzanthranyl*-10-*acetaldehyde*, and after purification through its *s*-trinitrobenzene *complex*, which crystallised from alcohol in vermilion needles, m. p. 149—150° (Found : C, 65·5; H, 3·9. $C_{20}H_{14}O,C_6H_3O_6N_3$ requires C, 65·7; H, 3·6%), it crystallised from alcohol in clusters of colourless needles, m. p. 150—151° (Found : C, 88·9; H, 5·6. $C_{20}H_{14}O$ requires C, 88·9; H, 5·2%). The *picrate* crystallised from benzene in feathery brick-red needles, m. p. 138·5—139·5°. Satisfactory analytical figures were not obtained (Found : C, 63·2; H, 3·7. $C_{20}H_{14}O,C_6H_3O_7N_3$ requires C, 62·5; H, 3·4%).

10-*Bromo*-9-*methyl*-1 : 2-*benzanthracene* was rapidly formed by bromination of 9-methyl-1 : 2-benzanthracene (Cook, Robinson, and Goulden, J., 1937, 393) in cold carbon disulphide. It crystallised from benzene in colourless plates, m. p. 122—123° (Found : C, 70·8; H, 4·15. $C_{19}H_{13}Br$ requires C, 71·0; H, 4·1%). The bromo-compound did not react with pyridine, as would be the case if substitution had occurred in the methyl group. Treatment with cuprous cyanide in phenylacetonitrile at 190—200° for 6 hours gave 10-*cyano*-9-*methyl*-1 : 2-*benzanthracene* (III; X = CN), which crystallised from acetic acid in yellow needles, m. p. 151·5—152° (Found : C, 90·15; H, 4·7 $C_{20}H_{13}N$ requires C, 89·85; H, 4·9%).

9-*Methyl*-1 : 2-*benz*-10-*anthraldehyde* (III; X = CHO).—Phosphorus oxychloride (1·1 g.) was added to a mixture of formomethylanilide (1·1 g.) and *o*-dichlorobenzene (1 c.c.). 9-Methyl-1 : 2-benzanthracene (1 g.) was then introduced, and the mixture heated on the water-bath for 2½ hours (compare Fieser and Hartwell, *loc. cit.*). The solution was poured into a solution of sodium acetate (5 g.) in water (100 c.c.), and the resinous product digested with a little ether and crystallised from acetic acid (charcoal). The *aldehyde* (0·35 g.) formed long golden-yellow needles, m. p. 111·5—112·5° (Found : C, 88·6; H, 5·2. $C_{20}H_{14}O$ requires C, 88·9; H, 5·2%).

10-*Bromo*-6-*methyl*-1 : 2-*benzanthracene* was obtained by bromination of 6-methyl-1 : 2-benzanthracene (Cook, J., 1932, 470) in carbon disulphide solution, and formed colourless lustrous plates, m. p. 138—139° (Found : C, 70·9; H, 4·1. $C_{19}H_{13}Br$ requires C, 71·0; H, 4·1%). This bromo-compound, which was oxidised by sodium dichromate in boiling glacial acetic acid to 6-methyl-1 : 2-benzanthraquinone, was converted by the standard treatment with cuprous cyanide in phenylacetonitrile into 10-*cyano*-6-*methyl*-1 : 2-*benzanthracene* (II; X = CN), which crystallised from acetic acid in flat yellow needles, m. p. 203·5—204·5° (Found : C, 90·1; H, 5·2. $C_{20}H_{13}N$ requires C, 89·85; H, 4·9%).

10-*Acetoxymethyl*-6-*methyl*-1 : 2-*benzanthracene*.—Hydrogen chloride was passed into a suspension of paraformaldehyde (0·4 g.) in acetic acid (25 c.c.) until a clear solution was obtained. 6-Methyl-1 : 2-benzanthracene (2·4 g.) and acetic acid (10 c.c.) were then added and the mixture was heated at 60° for 16 hours. The resulting chloromethyl compound was very soluble in benzene and could not be obtained crystalline. A washed benzene extract, filtered from sparingly soluble by-product, was evaporated, and the residue was boiled for 2 hours with potassium acetate (2·5 g.) in acetic acid (50 c.c.). This gave 10-*acetoxymethyl*-6-*methyl*-1 : 2-*benzanthracene* (1 g.), which crystallised from alcohol in colourless lustrous needles, m. p. 168·5—169·5° (Found : 84·3; H, 5·9. $C_{22}H_{18}O_2$ requires C, 84·1; H, 5·8%). Hydrolysis of this acetate with boiling alcoholic sodium hydroxide gave 10-*hydroxymethyl*-6-*methyl*-1 : 2-*benzanthracene* (II; X = CH_2·OH), which formed colourless silky needles (from benzene), decomposing at 220—230°, after sintering (Found : C, 88·0; H, 6·0. $C_{20}H_{16}O$ requires C, 88·2; H, 5·9%).

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