170. *The Synthesis of Growth-inhibitory Polycyclic Compounds. Part I.*

By G. M. Badger and J. W. Cook.

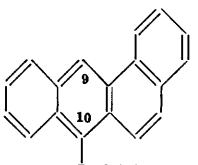
The discovery of Haddow that carcinogenic compounds have growth-inhibitory properties provides a basis for attempts to utilise compounds related to the carcinogenic hydrocarbons to control the growth of tumours. 10-*Chloromethyl*-1 : 2-*benzanthracene*, which is readily accessible by direct chloromethylation of 1 : 2-benzanthracene, has been utilised in the preparation of derivatives of the carcinogenic 10-methylbenzanthracene (type I) containing acidic, basic, and hydroxyl groups. It has also been found that the very rapidly acting carcinogenic 9 : 10-dimethyl-1 : 2-benzanthracene has high chemical reactivity in the methyl groups such as is possessed by 9 : 10-dimethylanthracene, and this observation has been utilised in the preparation of derivatives of type (III).

The observations of Haddow and his collaborators (Haddow and Robinson, *Proc. Roy. Soc.*, 1937, *B*, **122**, 442; Haddow, Scott, and Scott, *ibid.*, p. 477; Haddow, *J. Path. and Bact.*, 1938, **47**, 567, 581) on the action of carcinogenic hydrocarbons in inhibiting tumour-growth and body-growth have been extended over a wide range of carcinogenic compounds and related non-carcinogenic substances and it has been found that there is a good qualitative, but not a quantitative, correlation between the two types of biological action. In the present series of papers it is proposed to describe the synthesis of compounds related to the carcinogenic hydrocarbons in which it is hoped that the growth-inhibitory property may be emphasised and the tumour-producing property depressed. If this aim can be realised, it is evident that compounds of the type visualised would be worthy of consideration as therapeutic agents against cancer, and the search for suitable compounds with this in view is the primary objective of this series of investigations. Imperial Chemical Industries is also undertaking systematic research with this objective, under the direction of its Dyestuffs Group, and our own work is being planned in consultation with that body.

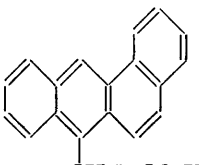
The study of carcinogenic polycyclic compounds has been mainly, but not entirely, confined to hydrocarbons. To avoid practical difficulties which would attend the therapeutic application of such substances it is proposed to concentrate attention on derivatives containing functional groups, particularly those which confer solubility in water. There is already evidence that certain functional derivatives of 1 : 2-benzanthracene have weak carcinogenic activity (see, for example, Shear, *Kongressbericht II des XVI. Internationalen Physiologen-Kongresses*, 1938, 64), and the present communication describes the synthesis of compounds related to the actively carcinogenic 10-methyl-1 : 2-benzanthracene, and also to 9 : 10-dimethyl-1 : 2-benzanthracene, which is the most rapidly acting carcinogenic compound yet found (see Bachmann, Kennaway, and Kennaway, *Yale J. Biol. and Med.*, 1938, **11**, 97). Such of our synthetic products as are suitable are being tested for growth-inhibitory action by Dr. A. Haddow, and also for carcinogenic action by Professor E. L. Kennaway. The results of these biological tests will be published elsewhere.

Chloromethylation of 1 : 2-benzanthracene with paraformaldehyde and hydrogen chloride in acetic acid solution (compare Darzens and Lévy, *Compt. rend.*, 1936, **202**, 74) or with chloromethyl ether in acetic acid solution (compare Vavon and Bolle, *ibid.*, 1937, **204**, 1826) gave good yields of 10-*chloromethyl*-1 : 2-*benzanthracene* (I), the orientation of which was shown by hydrogenation to 10-methyl-1 : 2-benzanthracene. The orientation of this compound is thus the same as that in other derivatives of 1 : 2-benzanthracene formed by direct substitution (Cook, J., 1930, 1089; Fieser *et al.*, *J. Amer. Chem. Soc.*, 1938, **60**, 1893, 2555). The chloromethyl compound (I; X = Cl) reacted with potassium acetate in acetic acid, giving 10-acetoxymethyl-1 : 2-benzanthracene, a compound previously obtained in poor yield by Fieser and Hershberg (*loc. cit.*, p. 1893), and this was hydrolysed to 10-*hydroxymethyl*-1 : 2-*benzanthracene* (I; X = OH), which has not hitherto been described, although Shear (*loc. cit.*) reports the slow production of tumours with a

sample of this compound stated by Fieser (*Amer. J. Cancer*, 1938, **34**, 100) to have been synthesised by von Braun and Kamp (unpublished). The high reactivity of the chlorine atom in 10-chloromethyl-1 : 2-benzanthracene is illustrated by the facts that 10-*ethoxymethyl*-1 : 2-*benzanthracene* (I; X = OEt) was obtained in good yield in an attempt to prepare the cyanomethyl compound with potassium cyanide in boiling alcoholic solution, and 10-acetoxymethyl-1 : 2-benzanthracene (I; X = OAc) was obtained in an attempt to transform the chloromethyl compound into 1 : 2-benz-10-anthraldehyde by boiling for 30 seconds with hexamethylenetetramine in acetic acid solution.* 10-Chloromethyl-1 : 2-benzanthracene reacted with pyridine to give 1 : 2-*benzanthranyl*-10-*methylpyridinium chloride* (I; X = C_5H_5NCl) and with piperidine to give N-(1 : 2-*benzanthranyl*-10-*methyl*)-*piperidine hydrochloride* (I; X = $C_5H_{10}N,HCl$).



(I.)



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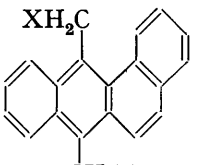

(III.)

Condensation of ethyl sodiomalonate with 10-chloromethyl-1 : 2-benzanthracene proceeded normally and gave *ethyl* (1 : 2-*benzanthranyl*-10-*methyl*)*malonate*, which passed, by hydrolysis and decarboxylation, into β-(1 : 2-*benz*-10-*anthranyl*)*propionic acid* (II).

10-Methyl-1 : 2-benzanthracene could not be chloromethylated, and was recovered unchanged after treatment which led to chloromethylation in the case of 1 : 2-benzanthracene. This is an indication of the extent of the steric hindrance at the other *meso*-position (9) of the 1 : 2-benzanthracene molecule. Anthracene, which is not subject to such steric hindrance, was readily chloromethylated to 9 : 10-*di*(*chloromethyl*)*anthracene*. Attempts to obtain chloromethyl derivatives from 9-methyl-1 : 2-benzanthracene, 3 : 4-benzpyrene, and 20-methylcholanthrene were unsuccessful. Reaction occurred in all three cases, but inseparable mixtures were formed, and it is probable that much of the difficulty was due to further condensation of the very reactive chloromethyl compounds which were presumably first formed.

Fieser (*Amer. J. Cancer*, 1938, **34**, 116) attaches considerable importance to the interesting observations made by him and Hershberg (*J. Amer. Chem. Soc.*, 1938, **60**, 1893, 2542) concerning the reactivity and position of attack in the oxidation of certain carcinogenic hydrocarbons with lead tetra-acetate. These workers found that 10-methyl-1 : 2-benzanthracene gave 10-acetoxymethyl-1 : 2-benzanthracene, but the yield was poor, possibly on account of the simultaneous formation of 9-acetoxy-10-methyl-1 : 2-benzanthracene. We have extended this reaction to the highly carcinogenic 9 : 10-dimethyl-1 : 2-benzanthracene. Substitution in both methyl groups took place with ease, and a good yield of 9 : 10-*di*(*acetoxymethyl*)-1 : 2-*benzanthracene* (III; X = OAc) was obtained; this was hydrolysed to 9 : 10-*di*(*hydroxymethyl*)-1 : 2-*benzanthracene* (III; X = OH). Such behaviour is reminiscent of the finding of Barnett and Matthews (*Ber.*, 1926, **59**, 1439) that 9 : 10-dimethylanthracene is brominated with great facility to the ωω'-dibromo-compound. It was found, moreover, that 9 : 10-dimethyl-1 : 2-benzanthracene likewise underwent bromination in carbon disulphide at — 10°, to give a *dibromo*-derivative which was converted by potassium acetate in acetic acid into the same diacetate (III; X = OAc) formed by direct oxidation of the hydrocarbon with lead tetra-acetate. The analogy between the two hydrocarbons was completed by a study of the oxidation with lead tetra-acetate of 9 : 10-dimethylanthracene, which led smoothly to 9 : 10-*di*(*acetoxymethyl*)-*anthracene*. Thus it is evident that high reactivity in the methyl groups is not specific to the carcinogenic hydrocarbon.

* Dr. C. L. Hewett (unpublished experiment) has found that 1-bromo-2-bromomethylnaphthalene is converted into 1-bromo-2-naphthaldehyde under these conditions.

Experimental.

1 : 2-*Benzanthracene*.—The following procedure for the cyclisation of *o*-1-naphthoylbenzoic acid to 1 : 2-benzanthraquinone and subsequent reduction to the hydrocarbon was found superior to those described in the literature: A mixture of *o*-1-naphthoylbenzoic acid (140 g.) and benzoyl chloride (140 c.c.) was heated to 130° and treated cautiously with concentrated sulphuric acid (4 c.c.) (compare Waldmann, *J. pr. Chem.*, 1938, **150**, 121). A vigorous reaction ensued with liberation of hydrogen chloride. Heating at 130° was continued until gas evolution ceased (about an hour); the hot solution was then poured into an excess of 6N-sodium hydroxide, and the whole boiled. The solid was collected and re-extracted with boiling dilute alkali solution, and the resulting quinone dried (yield, 122 g.). After recrystallisation from toluene it had m. p. 163—168° (lit., 168°).

For reduction, 1 : 2-benzanthraquinone (50 g.) was boiled under reflux for an hour with stannous chloride (150 g.) and concentrated hydrochloric acid (300 c.c.) in glacial acetic acid (500 c.c.). The cooled solution was diluted with water, and the resinous anthranol mixture was collected after an hour, by which time it had solidified, and was reduced to the hydrocarbon by 3 hours' boiling with 2N-sodium hydroxide (1 l.) and zinc dust (60 g.). After extraction of the zinc with hydrochloric acid the crude 1 : 2-benzanthracene was crystallised from glacial acetic acid and freed from coloured contaminants by boiling in benzene solution for an hour with one tenth of its weight of maleic anhydride. The benzene was removed by steam in the presence of dilute alkali solution, and the residual 1 : 2-benzanthracene was recrystallised from benzene. In this way 245 g. of colourless benzanthracene, m. p. 158—159° (lit. 160°), were obtained from 480 g. of benzanthraquinone.

10-*Chloromethyl*-1 : 2-*benzanthracene* (I; X = Cl).—Dry hydrogen chloride was passed into a suspension of paraformaldehyde (3·2 g.) in glacial acetic acid (100 c.c.) until solution was complete. 1 : 2-Benzanthracene (18·4 g.) and glacial acetic acid (80 c.c.) were then added and the suspension was heated at 60° for 20 hours. The cooled suspension was poured into water (500 c.c.) and the solid was collected and recrystallised from benzene. A by-product (2·3 g.), presumably 10 : 10′-*di*-(1 : 2-*benzanthranyl*)*methane*, remained undissolved; it separated from xylene as a white amorphous powder, m. p. above 300° (Found: C, 94·1; H, 5·4. $C_{37}H_{24}$ requires C, 94·8; H, 5·2%). 10-*Chloromethyl*-1 : 2-*benzanthracene* (15 g.; 68% yield), obtained from the benzene extract, crystallised from benzene in long, pale yellow needles, m. p. 186·5—187° (Found: C, 82·7; H, 4·9. $C_{19}H_{13}Cl$ requires C, 82·4; H, 4·7%).

The same chloromethyl compound was obtained in 70% yield when a suspension of 1 : 2-benzanthracene (46 g.) in glacial acetic acid (350 c.c.) and chloromethyl ether (20 g.) was heated at 80° for 24 hours.

Hydrogenation of 10-chloromethyl-1 : 2-benzanthracene in acetone solution with palladium-black was complete in 5 hours. The resulting 10-methyl-1 : 2-benzanthracene was purified by vacuum sublimation and crystallisation of its picrate, and the hydrocarbon and picrate were identified by direct comparison with authentic specimens (Cook, Robinson, and Goulden, J., 1937, 393).

10-*Hydroxymethyl*-1 : 2-*benzanthracene* (I; X = OH).—A solution of 10-chloromethylbenzanthracene (1 g.) and anhydrous potassium acetate (1 g.) in glacial acetic acid (50 c.c.) was boiled for 2 hours. The resulting acetate (1·1 g.) crystallised from methyl alcohol in clusters of snow-white needles, m. p. 148·5—149·5° (Fieser and Hershberg, *J. Amer. Chem. Soc.*, 1938, **60**, 1893, describe this acetate as pale greenish-yellow needles, m. p. 150·5—151·5°, corr.). Hydrolysis of the acetate with boiling alcoholic sodium hydroxide (2 hours) gave, in 96% yield, 10-*hydroxymethyl*-1 : 2-*benzanthracene* (I; X = OH), which crystallised from benzene in colourless silky needles, m. p. 170—172° (Found: C, 88·0; H, 5·7. $C_{19}H_{14}O$ requires C, 88·3; H, 5·5%). This carbinol slowly decomposes at 100°.

The *hydrogen succinate* was obtained when 10-hydroxymethyl-1 : 2-benzanthracene (2 g.) was heated at 100° for 9 hours with succinic anhydride (2 g.) in pyridine (10 g.). The acidic product was extracted with dilute sodium carbonate solution, and the reprecipitated acid was crystallised repeatedly from benzene and then toluene. The hydrogen succinate (0·8 g.) formed a colourless amorphous powder, m. p. 185·5—186° (Found: C, 77·3; H, 5·2. $C_{23}H_{18}O_4$ requires C, 77·1; H, 5·1%). 0·9 G. of hydroxymethylbenzanthracene was recovered from the neutral fraction.

10-*Ethoxymethyl*-1 : 2-*benzanthracene* (I; X = OEt) was obtained in an attempt to prepare the nitrile: A solution of 10-chloromethyl-1 : 2-benzanthracene (2·8 g.) in absolute alcohol (250 c.c.) was boiled under reflux with potassium cyanide (1 g.) for 3 hours. The ethoxy-

compound (2·1 g.) crystallised from alcohol in pale yellow, lustrous needles, m. p. 90—90·5° (Found: C, 87·9; H, 6·3. $C_{21}H_{16}O$ requires C, 88·0; H, 6·3%). The desired nitrile was obtained in unsatisfactory yield by means of cuprous cyanide, and improved conditions are being sought.

1 : 2-*Benzanthranyl*-10-*methylpyridinium Chloride* (I; X = C_5H_5NCl).—A suspension of 10-chloromethyl-1 : 2-benzanthracene (1 g.) in pure pyridine (4 c.c.) was kept at room temperature for 24 hours. The clear solution formed was poured into 25 c.c. of anhydrous ether and the precipitated hygroscopic *pyridinium chloride* was washed with dry ether and dried at 100° in a vacuum over phosphoric oxide (Found: N, 3·6. $C_{24}H_{18}NCl$ requires N, 3·9%). This chloride, m. p. 205—208° (decomp.), was very soluble in water and in alcohol, and could not be recrystallised. It was characterised by its sparingly soluble *picrate*, which crystallised from a large volume of water in bright yellow, microscopic, rectangular prisms, m. p. 199—201° (Found: N, 10·2. $C_{30}H_{20}O_7N_4$ requires N, 10·2%).

N-(1 : 2-*Benzanthranyl*-10-*methyl*)*piperidine Hydrochloride* (I; X = $C_5H_{10}N,HCl$).—A mixture of 10-chloromethyl-1 : 2-benzanthracene (3 g.) and piperidine (6 c.c.) was heated on the water-bath for an hour, and some of the excess of piperidine was removed under reduced pressure. Addition of concentrated hydrochloric acid (about 40 c.c.) gave an almost clear solution, from which the hydrochloride was precipitated by an equal volume of water. This was recrystallised from boiling water (charcoal). Further purification was effected by repeated crystallisation, carried out by dissolving the hydrochloride in the minimum amount of hot water and then adding concentrated hydrochloric acid in insufficient quantity to form a permanent turbidity. The *hydrochloride* crystallised on cooling, and after nine such treatments formed colourless lustrous needles (1·2 g.), m. p. 251—253° (decomp.) after darkening (Found: N, 3·9. $C_{24}H_{23}N,HCl$ requires N, 3·9%). The free base crystallised from alcohol in colourless needles, m. p. 106—107°.

Ethyl (1 : 2-*Benzanthranyl*-10-*methyl*)*malonate*.—10-Chloromethyl-1 : 2-benzanthracene (13 g.) was added, together with benzene (200 c.c.), to ethyl sodiomalonate prepared from ethyl malonate (15 g.) and sodium (1·5 g.) in benzene (100 c.c.). Reaction was allowed to proceed at room temperature overnight and was completed by 6 hours' boiling under reflux. The cooled benzene solution was extracted with water and concentrated on the water-bath under diminished pressure. The resulting oil subsequently solidified, and was recrystallised from alcohol. An insoluble *by-product* (1·2 g.) separated from its solution in benzene in colourless granules, m. p. 224—225° (Found: C, 87·2; H, 5·4%). The alcoholic solution gave *ethyl* (1 : 2-*benzanthranyl*-10-*methyl*)*malonate* (14·7 g.; 78% yield), which, after several recrystallisations from acetic acid and from alcohol, formed sheaves of stout colourless needles, m. p. 120—120·5° (Found: C, 77·8; H, 6·2. $C_{26}H_{24}O_4$ requires C, 78·0; H, 6·05%). The (1 : 2-*benzanthranyl*-10-*methyl*)*malonic acid* formed by hydrolysis with boiling alcoholic sodium hydroxide was purified through its *sodium* salt, which crystallised from dilute alcohol in lustrous colourless plates (Found: Na, 11·7. $C_{22}H_{14}O_4Na_2$ requires Na, 11·85%). The regenerated acid could not be obtained crystalline or constant-melting (m. p. *ca.* 200°) (Found: equiv., 170. Calc. for $\frac{1}{2}$ $C_{22}H_{16}O_4$: equiv., 172).

β-(1 : 2-*Benz*-10-*anthranyl*)*propionic Acid* (II).—The aforesaid malonic acid was decarboxylated by heating at 210—220° for ½ hour. The *monocarboxylic acid* (II) was purified through its sparingly soluble sodium salt and then recrystallised from acetic acid and from alcohol. It formed pale yellow, lustrous needles, m. p. 210—211° (Found: C, 84·0; H, 5·5. $C_{21}H_{16}O_2$ requires C, 84·0; H, 5·4%).

9 : 10-*Di*(*chloromethyl*)*anthracene*.—Anthracene (7·15 g.) and glacial acetic acid (45 c.c.) were added to a solution obtained by passing dry hydrogen chloride into a suspension of paraformaldehyde (3·2 g.) in glacial acetic acid (45 c.c.). The resulting suspension, heated at 60° for 20 hours, gave, after recrystallisation of the product from benzene, 9 : 10-*di*(*chloromethyl*)-*anthracene* (3 g.). After five recrystallisations from benzene this formed long, bright yellow needles, which decomposed, without melting, at 204—205° (Found: C, 69·85; H, 4·6. $C_{16}H_{12}Cl_2$ requires C, 69·8; H, 4·4%).

9 : 10-*Di*(*acetoxymethyl*)*anthracene*.—The 9 : 10-dimethylanthracene was obtained from 9 : 10-dimethoxy-9 : 10-dimethyl-9 : 10-dihydroanthracene (Guyot and Staehling, *Bull. Soc. chim.*, 1905, **33**, 1144) by shaking its solution in benzene–ether with sodium (compare Bachmann and Chemerda, *J. Amer. Chem. Soc.*, 1938, **60**, 1023). A mixture of 9 : 10-dimethylanthracene (0·5 g.), lead tetra-acetate (2·25 g.), and purified acetic acid (40 c.c.) was heated on the water-bath for 15 minutes, and the clear solution was poured into water. The flocculent precipitate was collected, washed, dried, and recrystallised from benzene. The

resulting 9 : 10-*di*(*acetoxymethyl*)*anthracene* (0·4 g.) was recrystallised from benzene and then alcohol, and formed long straw-yellow needles, m. p. 224—225° (Found : C, 74·8; H, 5·8. $C_{20}H_{18}O_4$ requires C, 74·5; H, 5·6%). Anthraquinone was obtained by oxidising this diacetate with chromic acid in boiling acetic acid, and the same diacetate was formed when the 9 : 10-di(chloromethyl)anthracene described above was treated with potassium acetate in boiling acetic acid.

9 : 10-*Di*(*bromomethyl*)-1 : 2-*benzanthracene* (III; X = Br).—A solution of bromine (1 c.c.) in carbon disulphide (10 c.c.) was slowly added to a solution of 9 : 10-dimethyl-1 : 2-benzanthracene (2·5 g.) (Bachmann and Chemerda, *loc. cit.*) in carbon disulphide (25 c.c.), cooled in a freezing mixture. Bromination took place instantaneously, and after ½ hour the crystalline product in suspension was collected, washed with dry ether, dried, and recrystallised from benzene. 9 : 10-*Di*(*bromomethyl*)-1 : 2-*benzanthracene* formed soft, pale yellow needles, m. p. 208—209° (Found : C, 57·9; H, 3·5. $C_{20}H_{14}Br_2$ requires C, 58·0; H, 3·4%), and was converted by potassium acetate in boiling acetic acid into the diacetate described below.

9 : 10-*Di*(*acetoxymethyl*)-1 : 2-*benzanthracene* (III, X = OAc).—9 : 10-Dimethyl-1 : 2-benzanthracene (3 g.) was heated on the water-bath for 15 minutes with lead tetra-acetate (13·5 g.) in purified acetic acid (225 c.c.). The crude precipitate formed by pouring into water was collected, dried, and digested with cold ether. The undissolved solid (2·25 g.) was recrystallised from benzene–light petroleum and then alcohol. 9 : 10-*Di*(*acetoxymethyl*)-1 : 2-*benzanthracene* (1·75 g.) formed pale yellow needles, m. p. 167—168° (Found : C, 77·5; H, 5·45. $C_{24}H_{20}O_4$ requires C, 77·4; H, 5·4%). For hydrolysis, a suspension of the diacetate (1 g.) in alcohol (25 c.c.) and 50% aqueous potassium hydroxide (2 c.c.) was boiled for an hour. After cooling, the resulting 9 : 10-*di*(*hydroxymethyl*)-1 : 2-*benzanthracene* (0·6 g.) was collected and recrystallised from alcohol; it formed a yellowish crystalline powder, m. p. 222—223° (Found : C, 82·9; H, 5·6. $C_{20}H_{16}O_2$ requires C, 83·3; H, 5·6%). The *dihydrogen disuccinate* was obtained in 85% yield when this diol (1·5 g.) was heated at 100° for 6 hours with succinic anhydride (3 g.) in pure pyridine (15 g.). It crystallised from alcohol in clusters of minute, pale yellow needles, m. p. 199·5—200·5° (Found : C, 68·8; H, 5·0. $C_{28}H_{24}O_8$ requires C, 68·9; H, 5·1%).

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