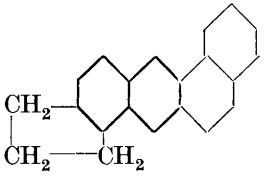
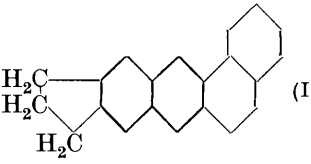
CCCLI.—*Polycyclic Aromatic Hydrocarbons. Part VII. 5 : 6-cyclo*Penteno*-1 : 2-benzanthracene, a Cancer-producing Hydrocarbon.*

By James Wilfred Cook.

In attempting to define the kind of molecular structure necessary for the development of cancer-producing activity, some condensed derivatives of 1 : 2-benzanthracene were prepared (this vol., p. 499). To secure greater diversity of type it was considered desirable to indicate the most probable structural formulæ for these hydrocarbons, and to reserve more complete chemical examination for any compounds which should prove active. Such a case has arisen in the substance described as *cyclo*pentenobenzanthracene. A 0·3% solution in benzene was applied twice weekly to the skin of 10 mice.* The mortality was high, only four mice remaining alive after 155 days. Two of these then bore tumours and a third mouse developed a tumour by the 178th day. One of the three tumours was shown to be an undoubted cancer, when the mouse died on the 220th day; the other two were papillomas which would probably have become malignant if the mice had lived longer.

*cyclo*Pentenobenzanthracene was further characterised by its *picrate* and *quinone* and the structure previously suggested (I) was confirmed by oxidation of the quinone to *anthraquinone*-1 : 2 : 5 : 6-*tetracarboxylic acid*, the orientation of which was proved by its formation from 1 : 2 : 5 : 6-dibenzanthraquinone, a substance of well-established constitution (Clar, *Ber.*, 1929, **62**, 357; compare Cook, this vol., p. 488).

(I.) 

 (II.)

An *isomeride* was isolated from the mother-liquors of 5 : 6-*cyclo*penteno-1 : 2-benzanthracene. This also was characterised by the preparation of its *picrate* and *quinone*, and is almost certainly 6 : 7-cyclo*penteno*-1 : 2-*benzanthracene* (II). A consideration of the intramolecular changes frequently encountered during the formation of hydrocarbons of this nature (this vol., pp. 487, 489) renders the only alternative 7 : 8-*cyclo*penteno-structure extremely improbable.

* I am indebted to Professor E. L. Kennaway for details of these preliminary animal experiments, which are being repeated and extended.—J.W.C.

The two hydrocarbons gave identical fluorescence spectra, similar to that of 1 : 2-benzanthracene (Hieger, private communication).

EXPERIMENTAL.

Isomeric cyclo*Pentenobenzanthracenes*.—The crude resinous ketone prepared from hydrindene (200 g.), 2-methyl-1-naphthoyl chloride (210 g.), and anhydrous aluminium chloride (210 g.) by the method previously described (this vol., p. 502) was heated at 450° for 2 hours, and the residue distilled in a vacuum. The distillate, b. p. 255—280°/7 mm., was dissolved in hot *cyclo*hexane, and the solution allowed to crystallise. The product, m. p. 125—170°, was twice recrystallised from benzene and yielded 6 g. of pure 5 : 6-*cyclo*penteno-1 : 2-benzanthracene (I), m. p. 199—200°.

The benzene-liquors were evaporated to dryness and the residue was recrystallised from *cyclo*hexane; it then had m. p. 135—141° (8·8 g.). The crystals were dissolved in acetic acid containing picric acid (15 g.); the *picrate* which separated was recrystallised 4 times from benzene and then formed bright red needles (3·2 g.), m. p. 180° (Found : C, 65·2; H, 4·1. $C_{21}H_{16},C_6H_3O_7N_3$ requires C, 65·2; H, 3·8%).

This picrate (of 6 : 7-*cyclo*penteno-1 : 2-benzanthracene) was shaken with benzene and dilute sodium carbonate solution, the benzene solution washed, dried with calcium chloride, and boiled with animal charcoal, and the benzene removed on the water-bath. The residual 6 : 7-cyclo*penteno*-1 : 2-*benzanthracene* (II) formed clusters of colourless needles, m. p. 164—165° (Found : C, 94·0; H, 6·2. $C_{21}H_{16}$ requires C, 94·0; H, 6·0%). Like its isomeride, this hydrocarbon gave a carmine solution in concentrated sulphuric acid.

6 : 7-cyclo*Penteno*-1 : 2-*benzanthraquinone*.—The aforesaid hydrocarbon, m. p. 164—165° (0·4 g.) was oxidised with sodium dichromate (0·8 g.) in boiling glacial acetic acid (10 c.c.), and the product sublimed at 220°/4 mm. The *quinone*, recrystallised from benzene–*cyclo*hexane, formed stout orange needles, m. p. 182—184° (Found : C, 84·3; H, 4·5. $C_{21}H_{14}O_2$ requires C, 84·6; H, 4·7%).

5 : 6-cyclo*Penteno*-1 : 2-*benzanthracene picrate* was prepared from the hydrocarbon, m. p. 199—200° (0·7 g.) and picric acid (1·5 g.) in acetic acid solution. It crystallised from benzene in chocolate-brown needles, m. p. 195° (Found : C, 65·2; H, 3·95. $C_{21}H_{16},C_6H_3O_7N_3$ requires C, 65·2; H, 3·8%).

5 : 6-cyclo*Penteno*-1 : 2-*benzanthraquinone* was prepared and purified in the same way as its isomeride. It formed orange needles, m. p. 184·5—185·5°, depressed by the isomeric quinone (Found : C, 84·4; H, 4·8. $C_{21}H_{14}O_2$ requires C, 84·6; H, 4·7%).

Anthraquinone-1 : 2 : 5 : 6-*tetracarboxylic Acid.*—(i) 1 : 2 : 5 : 6-Dibenzanthraquinone was successfully oxidised by the method employed by Scholl and Schwinger (*Ber.*, 1911, **44**, 2994) for the oxidation of 1 : 2-benzanthraquinone to anthraquinone-1 : 2-dicarboxylic acid. The dibenzanthraquinone (9 g.) was dissolved by gentle warming in concentrated sulphuric acid (100 c.c.), and the solution poured into water (360 c.c.). The almost boiling suspension was treated, gradually and with stirring, with powdered potassium permanganate (57 g.). Oxalic acid was then gradually added to destroy the manganese dioxide, and the orange suspension cooled and filtered. The solid was extracted with boiling aqueous ammonia, leaving a residue of unchanged dibenzanthraquinone (3·1 g.). The filtrate, on acidification, yielded a precipitate (3 g.), which was recrystallised from hot water. Analysis showed that the substance consisted essentially of the *tetracarboxylic acid*, but contained inorganic matter which could not be removed by recrystallisation. The acid was accordingly purified through its tetramethyl ester. For this purpose, the acid (3 g.) was dissolved in a slight excess of aqueous ammonia, and the hot solution treated with a solution of silver nitrate (5·5 g.). The dried silver salt (6·3 g.) was suspended in benzene (50 c.c.) and heated for 24 hours with methyl iodide (4 c.c.). The solid in suspension was collected and repeatedly extracted with boiling xylene. *Tetramethyl anthraquinone*-1 : 2 : 5 : 6-*tetracarboxylate*, which separated from the filtered solution, was recrystallised from xylene and obtained as a cream-coloured powder, m. p. 292—293°, very sparingly soluble in most media (Found : C, 59·7; H, 3·7. $C_{22}H_{16}O_{10}$ requires C, 60·0; H, 3·6%).

For hydrolysis, the ester (0·3 g.) was heated under reflux for 1 hour with potassium hydroxide (0·45 g.) in alcohol (75 c.c.). The potassium salt which separated was collected, dissolved in water, and again boiled for 1 hour with aqueous potassium hydroxide. The acid was precipitated by hydrochloric acid and recrystallised from boiling water. *Anthraquinone*-1 : 2 : 5 : 6-*tetracarboxylic acid* formed small, soft, cream-coloured needles which did not melt at 360° (Found : C, 56·0; H, 2·5. $C_{18}H_8O_{10}$ requires C, 56·3; H, 2·1%). It was sparingly soluble in hot water and could not be sublimed without decomposition. Both the acid and its tetramethyl ester gave the Liebermann anthraquinol reaction with zinc dust and alkali.

(ii) 5 : 6-*cyclo*Penteno-1 : 2-benzanthraquinone (0·75 g.) was oxidised with potassium permanganate (4·5 g.) exactly as described in the case of dibenzanthraquinone. The resulting acid was methylated through its silver salt, and yielded a substance which was in

every way identical with the above tetramethyl anthraquinone-1 : 2 : 5 : 6-tetracarboxylate.

The author desires to express his thanks to Mr. F. Goulden, who prepared the crude mixture of hydrocarbons used in this investigation.

THE RESEARCH INSTITUTE OF THE CANCER HOSPITAL (FREE),
LONDON, S.W. 3. [*Received, August 29th*, 1931.]