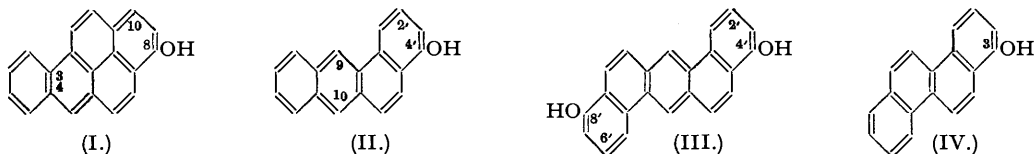


## 176. Polycyclic Aromatic Hydrocarbons. Part XXXII. 2'-Methoxy- and 2'-Methoxy-9 : 10-dimethyl-1 : 2-benzanthracene.

By G. M. BADGER.

2'-Methoxy-1 : 2-benzanthracene and 2'-methoxy-9 : 10-dimethyl-1 : 2-benzanthracene have been prepared by the scheme illustrated in formulæ (V—XII), for comparison with the (methylated) metabolic products of 1 : 2-benzanthracene and of 9 : 10-dimethyl-1 : 2-benzanthracene, in rabbits.

IN mice and rats, carcinogenic and related polycyclic hydrocarbons are metabolised to phenolic derivatives (I—IV) in which the hydroxy-group occupies the same relative position (Berenblum and Schoental, *Biochem. J.*, 1945, Proc. lxiv). In rabbits, however, 1 : 2 : 5 : 6-dibenzanthracene



is metabolised to a dihydroxy-derivative which differs from that obtained from mice and rats. This compound has not yet been identified, although several of the 55 possible isomers have been excluded (for references see Cason and Fieser, *J. Amer. Chem. Soc.*, 1940, **62**, 2681; 1941, **63**, 1256). The synthesis of all the remaining isomers would be a difficult task, and the present work was undertaken to provide a clue to the identity of the rabbit metabolite of dibenzanthracene. For this purpose, it was decided to prepare hydroxy-derivatives of 1 : 2-benzanthracene, which could then be compared with the metabolic products of this hydrocarbon, in rabbits. By analogy with dibenzanthracene, it is probable that the rabbit will metabolise benzanthracene to a hydroxy-derivative other than, or in addition to, the 4'-hydroxy-derivative.

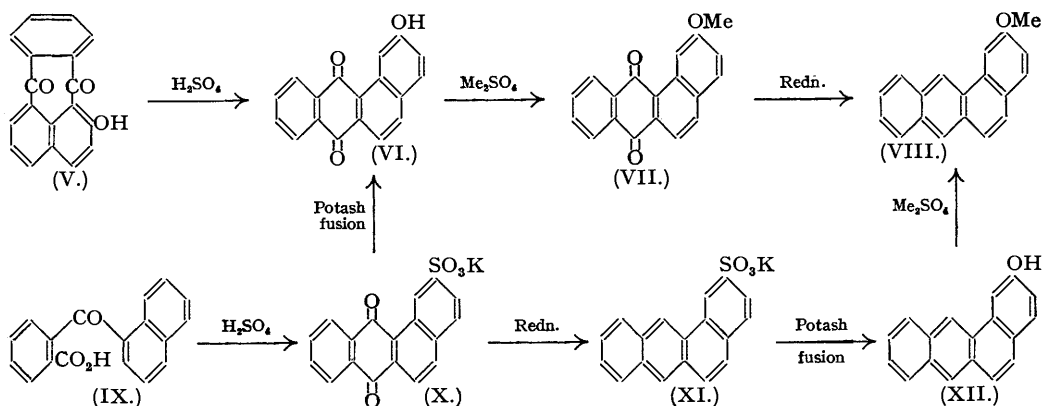
Since rats oxidise benzanthracene and dibenzanthracene at positions which are liable to chemical attack when the *meso*-positions are blocked (Cason and Fieser, *loc. cit.*), it appeared probable that the rabbit would oxidise the same compounds at some other positions which are also liable to chemical attack. In benzanthraquinone, this is the 2'-position, for Joffe and Fedorova (*J. Gen. Chem. Russia*, 1941, **11**, 619) have shown that, at high temperatures, benzanthraquinone is sulphonated at this position. (Other positions of the benzanthraquinone and benzanthracene molecules may also be subject to substitution reactions under certain conditions; see Scholl, *Ber.*, 1911, **44**, 2370; Cook and Hewett, *J.*, 1933, 1408.)

The fact that Berenblum and Schoental (*Cancer Res.*, 1946, **6**, 699) have confirmed the presence of 10-hydroxy-3 : 4-benzpyrene as well as 8-hydroxy-3 : 4-benzpyrene (I) in the excreta of both rats and rabbits, and that more of the 10-hydroxy-derivative is formed in the rabbit, lends added support to this view. For these reasons 2'-methoxy-1 : 2-benzanthracene and 2'-methoxy-9 : 10-dimethyl-1 : 2-benzanthracene have been prepared. The comparison of the former with the (methylated) rabbit metabolic products has been undertaken by Drs. Berenblum and Schoental. Such of the compounds as appear to be suitable will be tested for biological action by Professor A. Haddow. Results of these investigations will be published elsewhere.

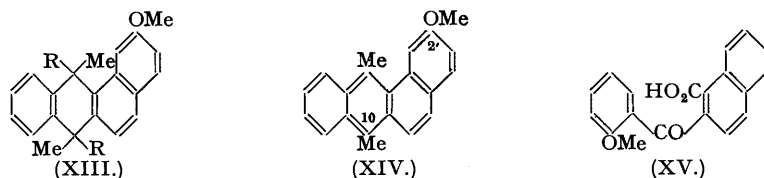
2'-Hydroxy-1 : 2-benzanthracene (XII) was prepared by sulphonation of 2-(1'-naphthoyl)-benzoic acid (IX), followed by reduction and potash fusion, a method substantially the same as that reported by Joffe and Fedorova (*loc. cit.*) except that naphthoylbenzoic acid was used instead of benzanthraquinone. Since the melting point of the final product (XII) did not agree with that reported by the Russian workers (although the melting points of the acetates were substantially in agreement), the scheme outlined in formulæ (V—XII) was carried out.

Phthaloylnaphthol (V) was converted into 2'-hydroxy-1 : 2-benzanthraquinone (VI) by the method of Fieser and Fieser (*J. Amer. Chem. Soc.*, 1933, **55**, 3342). The 50% yield claimed by these authors could not, however, be confirmed. In 35—40 runs, the yield of pure product averaged about 10%. The same compound was also prepared by fusion of potassium 1 : 2-benzanthraquinone-2'-sulphonate (X) with potassium hydroxide by the method of Joffe and Fedorova. Methylation with methyl sulphate gave 2'-methoxy-1 : 2-benzanthraquinone (VII), which was reduced with stannous chloride, followed by zinc and alkali, to 2'-methoxy-1 : 2-benzanthracene (VIII). The same compound was also prepared by methylation of 2'-hydroxy-1 : 2-benzanthracene obtained following the sulphonation of naphthoylbenzoic acid (IX—XII).

Treatment of 2'-methoxy-1:2-benzanthraquinone (VII) with methylmagnesium iodide gave 9:10-dihydroxy-2'-methoxy-9:10-dimethyl-9:10-dihydro-1:2-benzanthracene (XIII),



R = OH). Methylation with methyl alcohol and a trace of sulphuric acid gave 2':9:10-trimethoxy-9:10-dimethyl-9:10-dihydro-1:2-benzanthracene (XIII, R = OMe), which, on treatment with sodium, gave 2'-methoxy-9:10-dimethyl-1:2-benzanthracene (XIV) (cf. Bachmann and Chemerda, *J. Org. Chem.*, 1939, 4, 583; *J. Amer. Chem. Soc.*, 1938, 60, 1023).



The Friedel-Crafts reaction between phthalic anhydride and  $\beta$ -methoxynaphthalene, in tetrachloroethane solution, is known to give 2-(2'-hydroxynaphthoyl-1')-benzoic acid or its methyl ether (Fieser, *J. Amer. Chem. Soc.*, 1931, 53, 3546). When nitrobenzene is used as a solvent, the course of Friedel-Crafts reactions between  $\beta$ -methoxynaphthalene and various compounds, especially acyl chlorides, is modified, so that substitution occurs not at the 1-position but at the 6-position (for references, see Hudson, *J.*, 1946, 76). This does not appear to take place with aryl groups, for Hudson (*loc. cit.*) found that the anisoyl group enters the 1-position. The present work shows that phthalic anhydride also reacts at the 1-position, even in cold nitrobenzene solution. In an attempt to convert 2-(2'-hydroxynaphthoyl-1')-benzoic acid lactone into 2'-hydroxy-1:2-benzanthraquinone with sulphuric acid, only phthaloylnaphthol (V) and phthalic acid were formed. That the CO-bond at the 1-position should be broken under these conditions is of special interest in view of the conversion of phthaloylnaphthol into 1:2-benzanthraquinone.

In an attempt to prepare 5-hydroxy-1:2-benzanthracene, the Grignard solution from *o*-bromoanisole was condensed with 1:2-naphthalic anhydride. Attempts to prepare the benzanthraquinone from the resulting 2-(2'-methoxybenzoyl)-1-naphthoic acid (XV), by treatment either with sulphuric acid or with benzoyl chloride and a trace of sulphuric acid (Badger and Cook, *J.*, 1939, 802), were unsuccessful.

#### EXPERIMENTAL.

*2'-Hydroxy-1:2-benzanthraquinone.*—(i) This was prepared essentially as described by Fieser and Fieser (*loc. cit.*), but the yield claimed could not be confirmed. Phthaloylnaphthol (10 g.) was added to a solution of water (25 c.c.) and sulphuric acid (50 c.c.) and the mixture brought to the boil, with stirring. When oil separated, the mixture was poured on ice (200 g.). The product was extracted with a little boiling alcohol, and some unchanged phthaloylnaphthol filtered off. The crude 2'-hydroxy-1:2-benzanthraquinone obtained from the alcohol was dried, and refluxed for 1 hour with acetic anhydride and sodium acetate. The yellow needles which separated on cooling (1.6 g.) gave, on recrystallisation from acetic acid, 2'-acetoxy-1:2-benzanthraquinone, m. p. 254–255° (1 g.). The acetic acid liquors yielded colourless plates (0.4 g.) which after purification had m. p. 213–214°. This was evidently acetoxyphthaloylnaphthalene (Found: C, 76.1; H, 3.7. Calc. for C<sub>20</sub>H<sub>12</sub>O<sub>4</sub>: C, 76.0; H, 3.8%). Pure 2'-hydroxy-1:2-benzanthraquinone, m. p. 253–253.5°, was obtained from the acetate by hydrolysis with alcoholic sodium hydroxide followed by recrystallisation from alcohol.

(ii) A mixture of 2-(1'-naphthoyl)benzoic acid (15 g.) and concentrated sulphuric acid (150 c.c.) was heated on the water-bath for 1 hour, and then at 150—160° for 6 hours. The dark red solution was poured on ice (150 g.), and the sulphonic acid collected and sucked as dry as possible with the water-pump. The paste was dissolved in hot water, and the solution made alkaline with barium hydroxide. Potassium sulphate (5.1 g.) was added, and the mixture heated on the steam-bath for 2 hours. The filtrate, on evaporation to dryness, gave crude potassium 1 : 2-benzanthraquinone-2'-sulphonate (13.5 g.). After fusion with potassium hydroxide as described by Joffe and Fedorova (*loc. cit.*) this gave 2'-hydroxy-1 : 2-benzanthraquinone, identical with that prepared by the first method.

2'-Methoxy-1 : 2-benzanthraquinone.—2'-Hydroxy-1 : 2-benzanthraquinone (1.9 g.) was methylated in the usual way by the alternate addition of methyl sulphate and sodium hydroxide, at the temperature of the steam-bath, until a portion of the alkaline filtrate gave no precipitate with hydrochloric acid. Recrystallised from acetic acid, the 2'-methoxy-1 : 2-benzanthraquinone (1.83 g.) formed long golden-brown needles, m. p. 200—201° (Found : C, 79.3; H, 4.3.  $C_{19}H_{14}O_3$  requires C, 79.2; H, 4.2%).

2' : 9 : 10-Trimethoxy-1 : 2-benzanthracene.—2'-Hydroxy-1 : 2-benzanthraquinone (0.4 g.) was methylated with methyl sulphate and potassium hydroxide in the presence of zinc dust (2 g.) at 100°. The residue after filtration was extracted with boiling alcohol, and the alcohol decolourised with charcoal and concentrated. The 2' : 9 : 10-trimethoxy-1 : 2-benzanthracene (0.21 g.) formed almost colourless crystals, m. p. 173.5—175° (Found : C, 79.4; H, 5.4.  $C_{21}H_{18}O_3$  requires C, 79.3; H, 5.7%).

2'-Methoxy-1 : 2-benzanthracene.—(i) 2'-Methoxy-1 : 2-benzanthraquinone (0.25 g.), stannous chloride (1.5 g.), hydrochloric acid (3 c.c.) and acetic acid (5 c.c.) were boiled under reflux for 1 hour. The solution was poured into water, and after 1 hour the solid was transferred to a flask containing 2N-sodium hydroxide (15 c.c.) and zinc dust (1 g.). The mixture was boiled under reflux for 3½ hours, cooled, and filtered. The residue was extracted several times with boiling alcohol, and the solution concentrated and allowed to crystallise. The 2'-methoxy-1 : 2-benzanthracene (0.1 g.) formed almost colourless flat needles, m. p. 165—166° (Found : C, 88.4; H, 5.3.  $C_{19}H_{14}O$  requires C, 88.4; H, 5.4%). The alcoholic solution showed an intense blue fluorescence in daylight.

The *picrate*, prepared in alcohol, formed red-brown needles, m. p. 170—171° (Found : C, 61.9; H, 3.6; N, 8.7.  $C_{25}H_{17}O_5N_3$  requires C, 61.6; H, 3.5; N, 8.6%).

(ii) Potassium 1 : 2-benzanthraquinone-2'-sulphonate (7.5 g.) was reduced by 12 hours' boiling with zinc dust (14 g.) in water (300 c.c.) and ammonia (*d* 0.880; 75 c.c.). The resulting potassium 1 : 2-benzanthracene-2'-sulphonate (2.6 g.) was obtained as colourless plates from water. This salt (1.6 g.) was converted into the phenol by fusion at 290—300°, for 1 hour, with potassium hydroxide (8 g.). The 2'-hydroxy-1 : 2-benzanthracene (0.7 g.) formed pale yellow plates from acetic acid, m. p. 191.5—193.5° (lit. 178—179°) (Found : C, 88.5; H, 4.7. Calc. for  $C_{18}H_{12}O$  : C, 88.5; H, 4.9%). The acetate, prepared by refluxing a portion with acetic anhydride and sodium acetate, formed colourless silky needles, m. p. 156.5—158.5° (lit. 152—153°) (Found : C, 84.1; H, 4.8. Calc. for  $C_{20}H_{14}O_2$  : C, 83.9; H, 4.9%). The above hydroxybenzanthracene was methylated in almost quantitative yield by the alternate addition of methyl sulphate and sodium hydroxide. The product, crystallised from alcohol, was identical with the 2'-methoxy-1 : 2-benzanthracene prepared by the first method.

2' : 9 : 10-Trimethoxy-9 : 10-dimethyl-9 : 10-dihydro-1 : 2-benzanthracene.—2'-Methoxy-1 : 2-benzanthraquinone (2 g.), suspended in a Soxhlet thimble under the condenser (compare Bachmann and Chmerda, *J. Org. Chem.*, 1939, **4**, 583), dissolved after the Grignard solution [from methyl iodide (3 c.c.), ether (15 c.c.), and benzene (40 c.c.)] had been refluxed for 5 hours. After decomposition with ice-cold ammonium chloride, the organic layer was dried and evaporated. The gummy residue crystallised on stirring with benzene-light petroleum. 2'-Methoxy-9 : 10-dihydroxy-9 : 10-dimethyl-9 : 10-dihydro-1 : 2-benzanthracene (1.2 g.) formed colourless micro-crystals, from benzene, m. p. 157—160° (decomp.) (Found : C, 78.9; H, 6.3.  $C_{21}H_{20}O_3$  requires C, 78.8; H, 6.3%). The *methyl ether* was obtained by dissolving the diol in methyl alcohol and treating the cold solution with sulphuric acid (2 drops) in methyl alcohol (5 c.c.). It formed colourless needles, from methyl alcohol, m. p. 171—172° (Found : C, 79.4; H, 6.9.  $C_{23}H_{24}O_3$  requires C, 79.3; H, 6.9%).

2'-Methoxy-9 : 10-dimethyl-1 : 2-benzanthracene.—This was prepared by treatment of the above methyl ether with sodium (cf. Bachmann and Chmerda, *loc. cit.*). Recrystallised from methyl alcohol, 2'-methoxy-9 : 10-dimethyl-1 : 2-benzanthracene formed pale yellow lustrous plates, m. p. 112—113° (Found : C, 88.0; H, 6.3.  $C_{21}H_{18}O$  requires C, 88.1; H, 6.3%). Its alcoholic solution showed an intense blue fluorescence in daylight.

In one experiment a colourless compound, presumably the *photo-oxide*, was also isolated (cf. Sandin and Fieser, *J. Amer. Chem. Soc.*, 1940, **62**, 3098). It formed colourless needles from alcohol, m. p. 210—212° (after sintering) (Found : C, 79.25; H, 5.45.  $C_{21}H_{18}O_3$  requires C, 79.3; H, 5.7%).

2-(2'-Methoxynaphthoyl-1')-benzoic acid.—β-Methoxynaphthalene (7.5 g.), phthalic anhydride (8.0 g.), and nitrobenzene (100 c.c.) were cooled in ice and treated with aluminium chloride (12.5 g.) during 1 hour, with stirring. After 3 hours, the solution was kept at room temperature, with shaking, for 70 hours. After decomposition in the usual way, the acid was obtained; it crystallised from toluene as yellow prisms (4.5 g.), m. p. 191—194°. Its constitution was proved by demethylation with aluminium chloride in boiling benzene, followed by conversion into the lactone, m. p. 195—196° (Fieser, *J. Amer. Chem. Soc.*, 1931, **53**, 3546).

The same hydroxy-acid was obtained, in poor yield, following a similar experiment with β-naphthol.

Action of Sulphuric Acid on 2-(2'-Hydroxynaphthoyl-1')-benzoic Acid Lactone.—A solution of the lactone (1 g.) in concentrated sulphuric acid (10 c.c.) was heated at 60—70° for 6 hours, and then poured on ice. The solid obtained was dissolved in aqueous alcohol, from which phthaloylnaphthol, m. p. 196—197° (alone, or mixed with an authentic specimen) (0.06 g.), was obtained. The alcoholic liquors, on evaporation, deposited phthalic acid (0.26 g.), m. p. 196° (Found : C, 57.6; H, 3.7. Calc. for  $C_8H_6O_4$  : C, 57.8; H, 3.6%), converted into phthalic anhydride, m. p. 128—130°, by sublimation. Phthalic acid was also obtained following a similar experiment with the free acid. Both the free acid and the lactone gave cherry-red solutions in sulphuric acid.

2-(2'-Methoxybenzoyl)-1-naphthoic Acid.—A solution in ether (30 c.c.) and benzene (15 c.c.) of

*o*-anisylmagnesium bromide (from 25 g. of *o*-bromoanisole) was added slowly to a boiling solution of 1 : 2-naphthalic anhydride (26.4 g.) in anhydrous benzene (200 c.c.). The thick yellow precipitate was filtered off and decomposed with ice and dilute sulphuric acid in the presence of ether. The ether solution was extracted with sodium carbonate, and the *acid* precipitated (20 g.). After purification through the acetoxy-lactone, it formed colourless transparent prisms, m. p. 185—187° (Found: C, 74.45; H, 4.6.  $C_{19}H_{14}O_4$  requires C, 74.45; H, 4.6%). The *acetoxy-lactone*, prepared by heating the acid (20 g.) with acetic anhydride (40 c.c.) and pyridine (130 c.c.) on the steam-bath for 2 hours, formed colourless transparent prisms, from toluene, m. p. 209—211° (Found: C, 72.9; H, 4.7.  $C_{21}H_{16}O_5$  requires C, 72.4; H, 4.6%). Attempts to ring-close the acid with sulphuric acid, or with benzoyl chloride and a trace of sulphuric acid, were unsuccessful.

The author thanks Professor J. W. Cook, F.R.S., for his interest in this work, which has been made possible by the award of an Imperial Chemical Industries Research Fellowship. All analyses are microanalyses by Mr. J. M. L. Cameron.

UNIVERSITY OF GLASGOW.

[Received, October 7th, 1946.]

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