# THE SYNTHESIS OF 5-PHENYL-9,10-DIALKYL-9,10-DIHY-DROXY-9,10-DIHYDRO-1,2-BENZANTHRACENES AND RELATED COMPOUNDS\*

## W. E. BACHMANN AND JAMES T. BRADBURY

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Cook, Dodds, Hewett and Lawson<sup>1</sup> have found that certain 9,10-dialkyl-9,10-dihydroxy-9,10-dihydro-1,2,5,6-dibenzanthracenes (I) possess oes-



trogenic activity. The di-*n*-propyl derivative (I,  $R = n-C_3H_7$ ) of this series of diols was found to compare with oestriol in potency, as little as 0.025 mg. being sufficient to induce oestrus when injected into ovariectomized mice. In the course of testing a number of synthetic compounds for oestrogenic activity it was observed that tumors developed at the site of injection of 9,10-di-*n*-propyl-9,10-dihydroxy-9,10-dihydro-1,2,5,6dibenzanthracene. Of five rats injected subcutaneously four times with a solution of 0.4 mg. of the diol in sesame oil four developed sarcomas in six to seven months.<sup>2</sup>

Cook, Dodds, Hewett and Lawson reported that the carcinogenic hydrocarbons, 3,4-benzpyrene (formerly called 1,2-benzpyrene) and 5,6-cyclo-

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The nomenclature here employed is that believed by the authors to conform to the widest and most significant current usage; it does not adhere rigidly to the system of *Chemical Abstracts*.

<sup>1</sup> (a) Cook, Dodds, Hewett, and Lawson, Proc. Roy. Soc., **B114**, 272 (1934); (b) Cook, Dodds, and Lawson, *ibid.*, **B121**, 133 (1936).

<sup>2</sup> A more detailed account is presented by one of us (J. T. B.) in a preliminary report in the *University Hospital Bulletin*, **2**, 63 (1936), Ann Arbor, Michigan.

penteno-1,2-benzanthracene showed definite signs of oestrogenic activity. 9,10-Di-*n*-propyl-9,10-dihydroxy-9,10-dihydro-1,2-benzanthracene is an example of a potent oestrogenic compound possessing carcinogenic properties. This result led us to synthesize a number of diols of similar type in order to learn more about the relation between chemical structure and oestrogenic and carcinogenic activity. In this communication are described two diols obtained from 1,2-benzanthraquinone and three derived from 5-phenyl-1,2-benzanthraquinone.

Of the diols derivable from 1,2-benzanthraquinone only the di-*n*-butyl (II,  $R = n-C_4H_9$ ) and the diphenyl (II,  $R = C_6H_5$ ) derivatives have been prepared previously.<sup>16</sup> We have now prepared the dimethyl (II,  $R = CH_3$ )



and the diethyl (II,  $R = C_2H_b$ ) derivatives in crystalline form by interaction of 1,2-benzanthraquinone and the Grignard reagents from methyl iodide and ethyl bromide respectively. Although there is a possibility of the formation of two geometrical isomers, *cis* and *trans*, only one individual was obtained in each case.<sup>†</sup> The dimethyl diol was unable to induce oestrus but the diethyl compound proved to be active.<sup>‡</sup> In view of the marked carcinogenic activity of 10-methyl-1,2-benzanthracene<sup>3</sup> (III) it will be of interest to determine whether this property is destroyed or enhanced in 9,10-dimethyl-9,10-dihydroxy-9,10-dihydro-1,2-benzanthracene (II,  $R = CH_3$ ) and thus determine the effect of adding the extra methyl group and the two hydroxyl groups to the molecule.

Of the various possible phenyl-1,2-benzanthracenes only 6-phenyl-1,2benzanthracene has been prepared.<sup>4</sup> 5-Phenyl-1,2-benzanthracene has now been synthesized in the following manner. By interaction of phenyl-

<sup>&</sup>lt;sup>†</sup>COOK, DODDS, HEWETT, AND LAWSON, Ref. 1*a*, p. 275, reported the isolation of two 9,10-di-*n*-propyl-9,10-dihydroxy-9,10-dihydro-1,2,5,6-dibenzanthracenes and attributed the difference between them to stereoisomerism.

<sup>&</sup>lt;sup>‡</sup> A detailed account of the oestrogenic assays of the compounds described in this paper will be published elsewhere (*Proc. Soc. Exp. Biol. and Med.*).

<sup>&</sup>lt;sup>8</sup> FIESER AND NEWMAN, J. Amer. Chem. Soc., 58, 2376 (1936).

<sup>&</sup>lt;sup>4</sup> COOK, J. Chem. Soc., 1930, 1087.

magnesium bromide and 5-keto-5,6,7,8-tetrahydro-1,2-benzanthracene (IV) the carbinol, 5-phenyl-5-hydroxy-5,6,7,8-tetrahydro-1,2-benzanthracene (V), was obtained and the latter was smoothly dehydrated by potassium acid sulfate to 5-phenyl-7,8-dihydro-1,2-benzanthracene (VI). In view of the pronounced tendency of dihydronaphthalene<sup>5</sup> and dihydrophenanthrene<sup>6</sup> derivatives to become fully aromatic, it was anticipated that our dihydro derivative would be easily dehydrogenated, and this was found to be the case. Treatment of the dihydro compound with slightly more than the equivalent amount of sulfur at 250° for one hour gave the desired hydrocarbon, 5-phenyl-1,2-benzanthracene (VII).



Oxidation of the hydrocarbon by sodium dichromate and acetic acid yielded 5-phenyl-1,2-benzanthraquinone (VIII). With methylmagnesium iodide, ethylmagnesium bromide and *n*-propylmagnesium bromide the quinone gave the corresponding 5-phenyl-9,10-dialkyl-9,10-dihydroxy-9,10-dihydro-1,2-benzanthracenes (IX,  $R = CH_3$ ,  $C_2H_5$ ,  $n-C_3H_7$ ). The dimethyl diol appeared to be a mixture of the *cis* and *trans* forms but the ethyl and *n*-propyl derivatives proved to be single individuals. Here, too, the dimethyl derivative was inactive but the ethyl and *n*-propyl diols were capable of inducing oestrus.

The principal reaction taking place between 5-phenyl-1, 2-benzanthra-

<sup>5</sup> Cook and Hewett, *ibid.*, **1934**, 369.

<sup>6</sup> Cook and Hewett, *ibid.*, **1933**, 1105; Cohen, Cook, and Hewett, *ibid.*, **1935**, 1633.

quinone and phenylmagnesium bromide appeared to be a reduction of the quinone according to the following formulation:



Only a small amount of 5-phenyl-9,10-diphenyl-9,10-dihydroxy-9,10-dihydro-1,2-benzanthracene (IX,  $R = C_3H_5$ ) was formed. The relatively low yields of dialkyl diols obtained in most of the reactions may be due in part to this type of reaction and also to reduction of the quinone with formation of an alkene, a reducing action common to alkylmagnesium halides other than methylmagnesium halide.<sup>7</sup>

#### EXPERIMENTAL

9,10-Dimethyl-9,10-dihydroxy-9,10-dihydro-1,2-benzanthracene (II, R = CH\_2).-To a solution of the Grignard reagent prepared from 2.8 cc. of methyl iodide in 15 cc. of anhydrous ether and 15 cc. of benzene was added 2.58 g. (0.01 mole) of 1,2-benzanthraquinone. By pressing the rather insoluble quinone with a glass rod all of the solid was caused to react, and went into solution within twenty minutes at room temperature. Hydrolysis of the transparent tan-colored reaction mixture with icecold ammonium chloride solution after two hours and evaporation of the ether-benzene layer yielded an oil which crystallized when it was stirred with a mixture of benzene and petroleum ether. The colorless crystals (1.6 g.) were filtered off and recrystallized twice from benzene. 9,10-Dimethyl-9,10-dihydroxy-9,10-dihydro-1,2-benzanthracene crystallizes from benzene in diamond-shaped plates containing solvent of crystallization; this solvent is gradually lost when the crystals are exposed to air. From dilute alcohol the diol crystallizes in thin colorless plates without solvent of crystallization; m.p. 181.5-182.5°. With concentrated sulfuric acid the diol gives a dark red color. The diol is readily soluble in acetone and in alcohol, moderately soluble in benzene, and nearly insoluble in petroleum ether. For analysis all of the diols were dried at 100° at 0.2 mm. for several hours.

Anal. Calc'd for  $C_{20}H_{18}O_2$ : C, 82.7; H, 6.2.

Found: C, 82.7; H, 6.2.

9,10-Diethyl-9,10-dihydroxy-9,10-dihydro-1,2-benzanthracene (II,  $R = C_2H_3$ ).—On addition of 2.58 g. of 1,2-benzanthraquinone to the Grignard reagent from 3.3 cc. of ethyl bromide in 15 cc. of ether and 15 cc. of benzene an opaque dark reddish-brown solution resulted. Hydrolysis of the reaction mixture after two hours at room temperature and evaporation of the ether-benzene yielded an oil which crystallized when it was stirred with benzene-petroleum ether. The pale-yellow crystals were obtained entirely colorless by digestion with a hot aqueous solution of sodium hydrosulfite and sodium hydroxide, which removed traces of 1,2-benzanthraquinone. By three

<sup>&</sup>lt;sup>7</sup> KHARASCH AND WEINHOUSE, J. Org. Chem., 1, 209 (1936).

recrystallizations from benzene the 9,10-diethyl-9,10-dihydroxy-9,10-dihydro-1,2benzanthracene (1.7 g.) was obtained as long colorless needles; m.p. 145-145.5°. The diol gives a red color with concentrated sulfuric acid.

Anal. Calc'd for  $C_{22}H_{22}O_2$ : C, 83.0; H, 7.0.

### Found: C, 83.4; H, 6.9.

Reaction between 1,2-benzanthraquinone and n-propylmagnesium bromide.—Half a dozen trials using 2.58 g. of 1,2-benzanthraquinone and the Grignard reagent from 4 cc. of n-propyl bromide gave an oil which could not be induced to crystallize. Finally, one run in which only a half-hour was allowed for reaction gave a crystalline product (0.65 g.). From benzene-petroleum ether this product crystallized in colorless needles; m.p. 91-94° with effervescence. The product gave a dark-brown color with concentrated sulfuric acid. The analysis of the compound agreed not with that required by the diol but with the analysis of a ketone-carbinol formed by addition of a single propyl group to the quinone.

Anal. Calc'd for  $C_{21}H_{18}O_2$ : C, 83.2; H, 6.0.

Found: C, 83.2; H, 6.2.

5-Keto-5,6,7,8-tetrahydro-1,2-benzanthracene (IV).— $\beta$ -(3-Phenanthroyl)-propionic acid was prepared from phenanthrene and succinic anhydride by the Friedel and Crafts reaction in nitrobenzene according to the procedure of Haworth and Mavin.<sup>8</sup> When all the nitrobenzene had been removed from the hydrolyzed mixture by steam distillation, the residue was dissolved in a small amount of benzene; almost immediately crystallization of a mixture of  $\beta$ -(3-phenanthroyl)-propionic acid and  $\beta$ -(2phenanthroyl)-propionic acid took place. The crystals after being filtered and washed with benzene were nearly colorless. After being recrystallized from benzene the product was digested with boiling acetone (7 cc. per g.); this procedure dissolved the 3-isomer and left the 2-isomer (5% yield) as an insoluble residue. After recrystallization from toluene-acetic acid the  $\beta$ -(2-phenanthroyl)-propionic acid melted at 207-208°; Haworth and Mavin, who prepared this compound by another method but did not report its presence in the Friedel and Crafts reaction mixture, reported a value of 205-206°.

The  $\beta$ -(3-phenanthroyl)-propionic acid was reduced to  $\beta$ -(3-phenanthryl)-butyric acid by a combination of the procedures of Haworth and Mavin and of Martin.<sup>9</sup> A mixture of 25 g. of the keto acid, 75 g. of amalgamated granulated zinc (10-30 mesh), 25 cc. of toluene, 75 cc. of concentrated hydrochloric acid and 75 cc. of acetic acid was refluxed for twenty-four hours. During this time an additional 75 cc. of concentrated hydrochloric acid was added to the mixture in portions. The  $\gamma$ -(3-phenanthryl)-butyric acid obtained from the toluene layer was recrystallized from benzene; the first crop weighed 15 g. and melted at 136-138°. Another recrystallization from benzene raised the melting point of the product without much loss to 139-140°. From the mother liquor 5 g. of product melting at 110-120° was obtained; this material gave low yields of the cyclic ketone on cyclization. Cyclization of the acid was carried out according to the directions of Cook,<sup>10</sup> and the product, 5-keto-5,6,7,8tetrahydro-1,2-benzanthracene, was purified by vacuum distillation followed by recrystallization from chloroform-alcohol; from 20 g. of the acid 14 g. of the cyclic ketone was obtained.

5-Phenyl-5-hydroxy-5,6,7,8-tetrahydro-1,2-benzanthracene (V).-To an ice-cold

<sup>&</sup>lt;sup>8</sup> HAWORTH AND MAVIN, J. Chem. Soc., 1933, 1012.

<sup>&</sup>lt;sup>9</sup> MARTIN, J. Amer. Chem. Soc., 58, 1438 (1936).

<sup>&</sup>lt;sup>10</sup> COOK, J. Chem. Soc., 1933, 1597.

solution of phenylmagnesium bromide prepared from 13 g. of bromobenzene in 30 cc. of ether and 50 cc. of benzene was added 8.5 g. of 5-keto-5,6,7,8-tetrahydro-1,2-benzanthracene in portions. All of the ketone went into solution within ten minutes. After standing at room temperature for sixteen hours the clear solution was hydrolyzed with ice-cold ammonium chloride solution. From the ether-benzene solution an oil was obtained. On cooling a warm solution of the oil in alcohol, 8 g. of 5-phenyl-5-hydroxy-5,6,7,8-tetrahydro-1,2-benzanthracene crystallized. After a single recrystallization from acetone-alcohol the carbinol was obtained as colorless needles; m.p. 157-159° when the tube was put into the melting point bath at 150° (the melting point depends on the rate of heating for the compound decomposes in the neighborhood of its melting point). The carbinol is little soluble in alcohol but dissolves readily in benzene and in acetone. With concentrated sulfuric acid the carbinol gives a reddish-orange color.

Anal. Calc'd for C<sub>24</sub>H<sub>20</sub>O: C, 88.9; H, 6.2.

Found: C, 88.9; H, 6.2.

In the mother liquor at least 0.6 g. of carbinol was present, for this amount of dihydro compound was obtained from it by dehydration.

5-Phenyl-7,8-dihydro-1,2-benzanthracene (VI).—A mixture of 8 g. of the aforementioned carbinol and 12 g. of powdered potassium acid sulfate was heated at 160° for one hour. After removal of the inorganic salt by means of water, the dihydro compound was recrystallized from acetone-alcohol, from which it was obtained in colorless needles; yield, 7.8 g.; m.p. 125–126°.

Anal. Calc'd for C24H18: C, 94.1; H, 5.9.

Found: C, 94.1; H, 5.9.

5-Phenyl-1, 2-benzanthracene (VII).—A mixture of 6.2 g. of the dihydro compound and 1 g. of sulfur was heated at 250° for one hour. Some copper powder was added to the hot mixture in order to combine with the excess of sulfur and the 5-phenyl-1, 2benzanthracene was distilled from the mixture at 0.2 mm. By recrystallization from acetone-alcohol the hydrocarbon was obtained as cream-colored needles; yield, 5.22 g.; m.p. 151-152°; by purification through the picrate the hydrocarbon was obtained colorless without change in melting point. From acetic acid the hydrocarbon was obtained in the form of stout highly-refracting needles. 5-Phenyl-1,2-benzanthracene is little soluble in cold or hot alcohol but dissolves readily in hot acetone and benzene. Unlike 6-phenyl-1,2-benzanthracene which gives a crimson color with concentrated sulfuric acid, 5-phenyl-1,2-benzanthracene gives no color with this acid.

Anal. Calc'd for C24H16: C, 94.7; H, 5.3.

Found: C, 94.5; H, 5.2.

The *picrate* of 5-phenyl-1,2-benzanthracene crystallizes from benzene in brick-red needles; m.p. 165-166°.

Anal. Calc'd for  $C_{24}H_{16}$ ·  $C_{6}H_{3}O_{7}N_{3}$ : N, 7.9. Found: N, 7.9.

5-Phenyl-1, 2-benzanthraquinone (VIII).—A mixture of 5.06 g. of 5-phenyl-1, 2benzanthracene and 6.6 g. of sodium dichromate dihydrate in 100 cc. of acetic acid was kept at the boiling point of the solution for fifteen minutes. After addition of an equal volume of dilute sulfuric acid the quinone which precipitated was collected by filtration and recrystallized from xylene-alcohol or from acetone-alcohol; from either of these solvents the 5-phenyl-1,2-benzanthraquinone was obtained as golden-yellow needles; yield, 5.16 g.; m.p. 188–188.5°. Purification of a sample by means of hot sodium hydrosulfite and sodium hydroxide solution (which gives a red vat) raised the melting point to 189–189.5°. The quinone is practically insoluble in cold alcohol or acetic acid; it is moderately soluble in hot acetone and very soluble in hot xylene. With concentrated sulfuric acid the quinone gives a reddish-brown color.

Anal. Cale'd for  $C_{24}H_{14}O_2$ : C, 86.2; H, 4.2.

Found: C, 86.4; H, 4.4.

5-Phenyl-9,10-dimethyl-9,10-dihydroxy-9,10-dihydro-1,2-benzanthracene (IX,  $R = CH_3$ ).—A transparent tan-colored solution resulted from interaction of 1.1 g. of 5-phenyl-1,2-benzanthraquinone and the Grignard reagent from 1.3 cc. of methyl iodide in 16 cc. of a 1:1 mixture of ether and benzene. The product, which was obtained by hydrolysis of the clear solution after one hour at room temperature, crystallized when it was stirred with benzene-petroleum ether. Two recrystallizations from benzene gave colorless ill-defined crystals (0.3 g.) which were probably a mixture of the *cis* and *trans* diols; m.p. 160-164°. By recrystallization from dilute alcohol a small quantity of a homogeneous product was obtained which melted at about 130°, the melt quickly solidified and the solid then remelted at 215-216°. A violet color was formed on mixing the diol with concentrated sulfuric acid.

Anal. Calc'd for C<sub>26</sub>H<sub>22</sub>O<sub>2</sub>: C, 85.2; H, 6.1.

Found: C, 85.9; H, 5.7.

5-Phenyl-9,10-diethyl-9,10-dihydroxy-9,10-dihydro-1,2-benzanthracene (IX,  $R = C_2H_b$ ).—A dark reddish-brown solution resulted on mixing 1.1 g. of 5-phenyl-1,2benzanthraquinone and the Grignard reagent from 1.5 cc. of ethyl bromide in 16 cc. of ether-benzene (1:1). On working up the mixture as described for the methyl homologue the diol was obtained as colorless crystals (0.26 g.). From benzene the diol crystallized in long, colorless needles which contained solvent of crystallization. From dilute alcohol the diol was obtained in long, thin, narrow colorless plates; m.p. 147.5-148°. The diol gives a blue color with concentrated sulfuric acid.

Anal. Calc'd for C<sub>28</sub>H<sub>26</sub>O<sub>2</sub>: C, 85.2; H, 6.6.

Found: C, 85.5; H, 6.5.

5-Phenyl-9, 10-di-n-propyl-9, 10-dihydroxy-9, 10-dihydro-1, 2-benzanthracene (IX,  $R = n-C_3H_7$ ).—The opaque dark reddish-brown color of the solution resulting from interaction of 1.1 g. of 5-phenyl-1, 2-benzanthraquinone and the Grignard reagent from 2 cc. of *n*-propyl bromide in 16 cc. of ether-benzene (1:1) gradually disappeared, and after a few hours at room temperature the solution was transparent and had a tan color. Hydrolysis in the usual manner yielded 0.25 g. of the diol, which crystallized from benzene in long, colorless needles. From dilute alcohol the diol crystallizes in long, thin, narrow, colorless plates; m.p. 191.5-192.5°. On mixing the diol with concentrated sulfuric acid a blue color formed.

Anal. Calc'd for C<sub>30</sub>H<sub>30</sub>O<sub>2</sub>: C, 85.3; H, 6.7.

Found: C, 85.0; H, 6.9.

The yellow oily by-product obtained in the reaction was heated with 0.8 g. of sodium dichromate dihydrate in 10 cc. of acetic acid for ten minutes. The solution was poured into dilute sulfuric acid, and the precipitate was filtered off, washed with water and with methanol. By recrystallization from acetone-alcohol 0.45 g. of pure 5-phenyl-1,2-benzanthraquinone was obtained.

Reaction between 5-phenyl-1, 2-benzanthraquinone and phenylmagnesium bromide.— To the Grignard reagent from 1.6 cc. of bromobenzene in 16 cc. of ether-benzene (1:1) was added 1.1 g. of 5-phenyl-1,2-benzanthraquinone. After a short time a clear solution was obtained, but after a few hours a large quantity of solid precipitate was present. After twelve hours the mixture was hydrolyzed with ammonium chloride solution. A considerable amount of insoluble brown-black solid remained suspended in the ether-benzene layer; from this solid 0.46 g. of 5-phenyl-1,2-benzanthraquinone was isolated by means of sodium hydrosulfite and sodium hydroxide. The residue left on evaporation of the ether-benzene solution was treated with hot alcohol; 0.34 g. of quinone remained undissolved, making a total recovery of 0.8 g. (73%) of 5-phenyl-1,2-benzanthraquinone. The residue obtained by evaporation of the alcoholic solution was sublimed at 80°/0.2 mm.; the sublimate consisted of pure biphenyl (0.48 g.). From the non-volatile residue a small quantity of colorless crystals was isolated by recrystallization from benzene. This product, presumably 5-phenyl-9, 10-diphenyl-9, 10-dihydroxy-9, 10-dihydro-1, 2-benzanthracene, melted at about 240° with decomposition; the amount was too small to purify.

#### SUMMARY

Two new 9,10-dialkyl-9,10-dihydroxy-9,10-dihydro-1,2-benzanthracenes have been synthesized, one of which is capable of inducing oestrus in ovariectomized mice.

5-Phenyl-1, 2-benzanthracene has been synthesized, and from it three 5-phenyl-9, 10-dialkyl-9, 10-dihydroxy-9, 10-dihydro-1, 2-benzanthracenes have been prepared, of which two possess oestrogenic activity.