by crystallization from petroleum ether and methanol. The melting point of a mixture of this base and the petroleum product showed no depression.

Summary

Two benzo[h]quinoline homologs have been isolated from California petroleum. Their structures, formulated as 2,3-dimethylbenzo[h]quinoline and 2,4-dimethylbenzo[h]quinoline, respectively, have been confirmed by synthesis.

AUSTIN, TEXAS RECEIVED MAY 26, 1941

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Synthesis of 2-Hydroxy-3,4-benzpyrene and 2-Methyl-3,4-benzpyrene

BY LOUIS F. FIESER AND HANS HEYMANN

References to syntheses of the 2′-, 3′-, 4′-, 5-, and 6-monomethyl derivatives of 3,4-benzpyrene have been summarized in a paper[1] reporting the synthesis of a sixth isomer (9-methyl). In the series of monohydroxy compounds, the 4′-,[2] 5-[3] and 6-[4]isomers have been synthesized for biological testing. Apart from the preparation of 5-derivatives by direct substitution of the hydrocarbon, these substances have been produced by syntheses in which the 3,4-benzpyrene ring system is elaborated starting with pyrene (3′- and 4′-CH_3, 4′-OH), perinaphthane or a homolog (2′-, 3′-, 5-, 6- and 9-CH_3), or a chrysenoid intermediate (6-OH). The present paper reports syntheses of 2-derivatives from 1′-keto-1′,2′,3′,4′-tetrahydro-1,2-benzanthracene (V) as the essential intermediate. The fifth ring was built on by orthodox reactions, but the intermediate was prepared by a novel method which offers opportunities for additional synthetic applications.

1′-Keto-1′,2′,3′,4′-tetrahydro-1,2-benzanthracene was prepared by Cook and Robinson[5] by the cyclization of γ-2-anthrylbutyric acid (IV), which they obtained from anthracene in 9% overall yield by succinoylation and reduction, as reported from this Laboratory.[6] As an alternate route, we investigated the application of the phthalic anhydride synthesis to γ-phenylbutyric acid. Although the ethyl ester of this substance failed to enter into the Friedel and Crafts reaction in nitrobenzene, tetrachloroethane or carbon bisulfide solution, it was found that the acid itself can be condensed satisfactorily with phthalic anhydride in tetrachloroethane in the presence of three equivalents of aluminum chloride. As in a recorded instance,[7] the use of slightly deteriorated aluminum chloride facilitated the purification of the product. The keto acid I was separated easily as a complex and isolated pure in 58% yield.

For the reduction of the carbonyl group of I, the method of hydrogenation over copper chromite without solvent, which has been applied with success to monobasic keto acids,[8] gave even moderate yields only when conducted on a small scale, and it was subject to the difficulty that the keto diacid destructively attacked the catalyst and gave chromium-contaminated material. Reduction with zinc dust and alkali gave only resinous material. It was found that the reduction can be accomplished very smoothly by hydrogenation over copper chromite in a weakly alkaline aqueous medium.[9]

Cyclization of the diphenylmethane diacid II was accomplished more satisfactorily with hydrogen fluoride than with sulfuric acid and gave a product characterized as the anthrone acid III by reduction to the known anthrylbutyric acid IV. That the diacid yields an anthrone rather than a tetralone derivative is in line with observations on the relative ease of formation of these ring systems in non-competitive instances (zinc chlo-

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[1] Fieser and Novello, THIS JOURNAL, **62**, 1855 (1940).

[2] Fieser, Hershberg and Newman, *ibid.*, **57**, 1509 (1935).

[3] Fieser and Hershberg, *ibid.*, **60**, 2542 (1938); **61**, 1565 (1939).

[4] Fieser and Johnson, *ibid.*, **62**, 575 (1940).

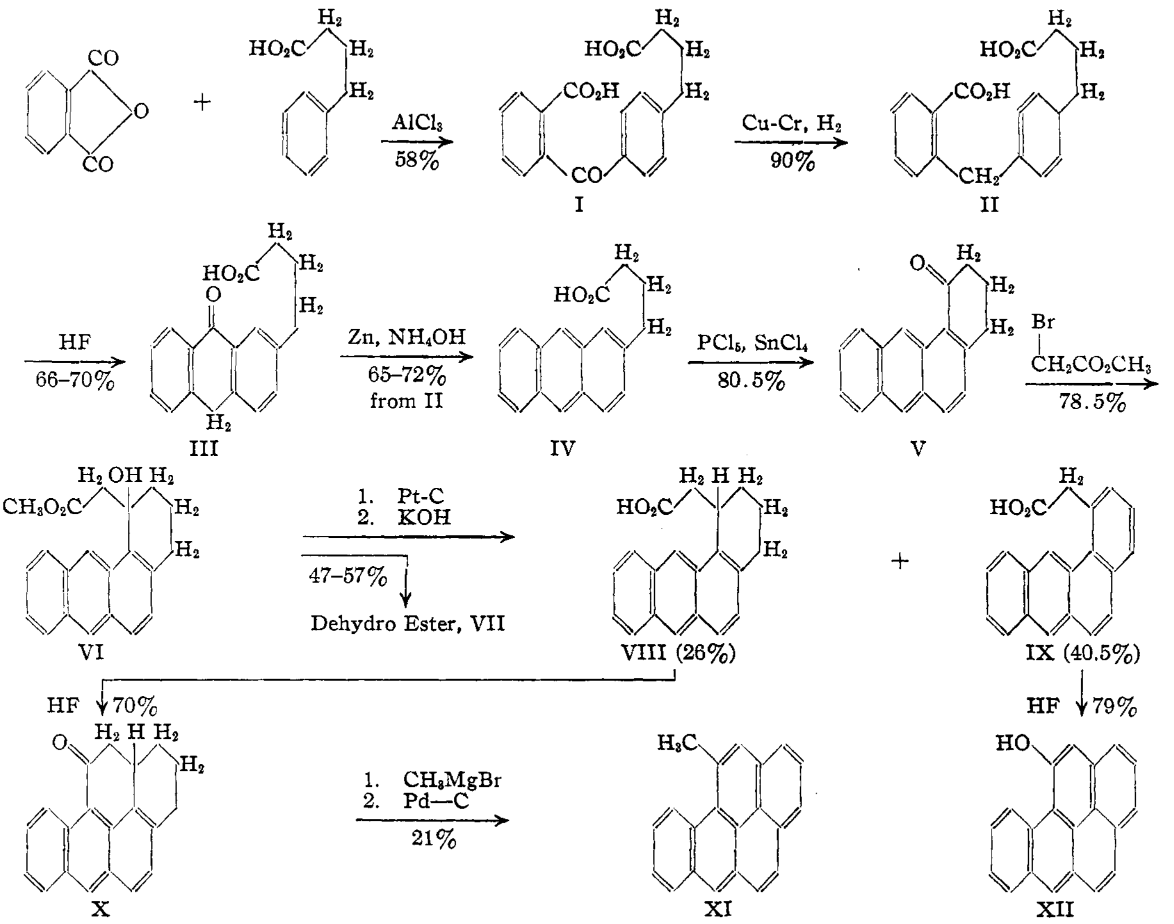
[5] Cook and A. M. Robinson, *J. Chem. Soc.*, 505 (1938).

[6] Fieser and Peters, THIS JOURNAL, **54**, 4355 (1932). The procedures were not described in detail in this paper and the yield reported for the succinoylation was miscalculated. We used over twice the proportion of aluminum chloride employed by Cook and Robinson (150 g. for 89 g. of anthracene) and obtained yields of 21 and 22% (C. and R., 13%). Like Cook, Robinson and Roe, *J. Chem. Soc.*, 266 (1939), we investigated the succinoylation of 9,10-dihydroanthracene; in this case the use of 2.2 times the amount of aluminum chloride employed by the English investigators apparently altered the course of the reaction, for the sole acidic product encountered was β-2-anthroylpropionic acid (11% yield).

[7] Scholl, Dehnert and Wanka, *Ann.*, **493**, 57 (1932).

[8] Fieser and Hershberg, THIS JOURNAL, **59**, 1028 (1937).

[9] Subsequent to this observation, the method was applied successfully in other instances already reported: Fieser and Cason, *ibid.*, **62**, 1293 (1940); Fieser and Clapp, *ibid.*, **63**, 319 (1941); Fieser and Daudt, *ibid.*, **63**, 782 (1941). The hydrogenation of aliphatic keto acids to hydroxy acids in alkaline solution is described by Allen, Wyatt and Henze, *ibid.*, **61**, 843 (1939).



ride method[8,10]). The anthrone can be obtained as nearly colorless crystals from non-fluorescent benzene solutions, but it rapidly turns yellow and deteriorates when warmed in hydroxylic solvents; the latter solutions exhibit fluorescence indicative of the presence of the enolic form. The solution of the acid in sodium carbonate is deep yellow-brown, and even the methyl ester dissolves to some extent in cold soda solution to give a yellow color. Thus the substance has a greater tendency to enolize than anthrone itself[11] and is consequently more sensitive to secondary changes.

The reduction of the anthrone acid III was accomplished most satisfactorily with zinc and ammonium hydroxide; when alkali was used the separation of the sparingly soluble and gelatinous sodium salt of the reduction product tended to impede the reaction. It is advantageous to employ the crude, wet cyclization product for the reduction, and in this case the yield from II is good. The over-all yield of γ-2-anthrylbutyric acid (IV) from γ-phenylbutyric acid is 34–38%, which is three or four times the yield in the synthesis starting with anthracene. Cook and Robinson[5] cyclized the acid IV both by heating it with stannic chloride and by treatment of the acid chloride with aluminum chloride, but in our hands neither method gave satisfactory results. When the ring closure was effected by the action of stannic chloride on the acid chloride, pure 1′-keto-1′,2′,3′,4′-tetrahydro-1,2-benzanthracene (V) was isolated easily in excellent yield. Cyclization with hydrogen fluoride gave neutral material in high yield, but the product appeared to be a mixture of V with the linear isomer.

After much experimentation it was found that the Reformatsky condensation of the keto tetrahydrobenzanthracene V and methyl bromoacetate can be carried out at the reflux temperature of a 1:6 mixture of ether and benzene; stirring of the mixture prevents separation of the addition complex as a gum, which coats the surface of the

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[10] Fieser and Hershberg, THIS JOURNAL, **60**, 1893 (1938); **61**, 1272 (1939).

[11] K. H. Meyer, *Ann.*, **379**, 37 (1911).

zinc, and keeps it in suspension in the form of a granular precipitate. The resulting carbinol VI is easily isolated in a crystalline, analytically pure condition. It undergoes dehydration on being melted, and may be converted by this method in 53.5% yield into a dehydro ester in which the position of the newly formed double bond has not been determined. Similar yields of the unsaturated ester or the corresponding acid were obtained on conducting the dehydration with formic acid or with phosphorus oxychloride in pyridine,[12] or by the action of thionyl chloride followed by treatment with alcoholic potash.[13] Treatment with hydrogen fluoride gave an unstable intermediate which when heated afforded a small amount of the impure unsaturated ester.

Since no method of dehydration was found whereby the unsaturated ester or acid could be obtained in more than moderate yield, the Reformatsky product VI was submitted directly to dehydrogenation, following the method of Bachmann.[14] The reaction was conducted by the Linstead technique[15] with the use of platinized charcoal in a boiling solution of α-methylnaphthalene contained in a special apparatus of minimum gas space from which the evolved hydrogen could be swept with pure carbon dioxide into an azotometer. The gas evolution stopped after the accumulation of only 28.5% of the amount calculated for the loss of two hydrogen atoms and, after hydrolysis of the reaction mixture, the yield of 1,2-benzanthryl-1′-acetic acid (IX) was only 40.5%. As a by-product there was isolated 26% of 1′,2′,3′,4′-tetrahydro-1,2-benzanthryl-1′-acetic acid (VIII), which was separated readily from the main product by crystallization. Evidently the intermediate dihydride resulting from the loss of water from the carbinol undergoes concurrent dehydrogenation and disproportionation, and indeed the products VIII and IX were obtained in similar yields starting with the pure dihydride. It was established in a separate experiment that the tetrahydro ester, once formed, undergoes only very slow and partial dehydrogenation in boiling α-methylnaphthalene. The stability of this substance appears more unusual than the tendency of the dihydride to suffer disproportionation.[15,16]

Pure 2-hydroxy-3,4-benzpyrene (XII) was obtained in excellent yield by the cyclization of the aromatized acid IX with hydrogen fluoride. The substance, which is best characterized in the form of the sharply melting acetate, is soluble in dilute alkali, couples with diazotized *p*-nitroaniline, and gives strongly fluorescent solutions in organic solvents which undergo discoloration on exposure to the air. The spectrum of the hydroxy compound, kindly determined by Dr. R. N. Jones, closely resembles that of the parent hydrocarbon.

The isolation of the tetrahydro acid VIII as a product of disproportionation offered a route to 2-methyl-3,4-benzpyrene. An attempt to prepare this acid by the reduction of the Reformatsky product VI with hydrogen iodide and phosphorus proved unsuccessful and led only to a high melting amorphous product. The carbinol on hand was therefore dehydrated by heat and the unsaturated ester submitted to hydrogenation in the presence of Adams catalyst. Unfortunately the reaction did not stop at the desired stage but continued until about two moles of gas had been consumed. Since the desired tetrahydride VIII had been found resistant to dehydrogenation in boiling α-methylnaphthalene, the oily hydrogenation product was treated with platinized charcoal under these conditions and indeed the acid VIII was isolated after hydrolysis, in 24% over-all yield. Alternate methods of preparation were not explored because the material thus obtained sufficed for completion of the synthesis. Cyclization of VIII with hydrogen fluoride gave the saturated, non-enolic ketohexahydrobenzpyrene X, and this was converted to the methyl carbinol and the crude reaction product dehydrogenated as above in boiling α-methylnaphthalene. A pure hydrocarbon which gave the correct analysis for 2-methyl-3,4-benzpyrene (XI) was isolated without difficulty.

2-(γ-Carboxypropyl)-anthrone-9 (III) was investigated as a possible starting point for the synthesis of the as yet unknown 1′,9-dimethyl-1,2-benzanthracene. The necessary first step, consisting in the introduction of a 9-methyl group, was indeed accomplished, but in such low and variable yield that the enterprise was abandoned. 9-Methylanthryl-2-butyric acid (XIII) was obtained at best in 10–17% yield, and usually was accompanied by the anthraquinone arising from the oxidation of III.

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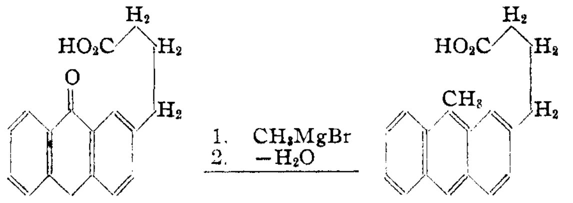
[12] Butenandt and Schmidt-Thomé, *Ber.*, **71**, 1487 (1938); **72**, 182 (1939).

[13] Bachmann, Cole and Wilds, THIS JOURNAL, **62**, 824 (1940).

[14] Bachmann, *ibid.*, **60**, 624 (1938).

[15] Linstead, Millidge, Thomas and Walpole, *J. Chem. Soc.*, 1146 (1937).

[16] Linstead, Michaelis and Thomas, *ibid.*, 1139 (1940).



III XIII

This is analogous to the results of the attempted Grignard methylation of 1′-methyl-1,2-benzanthrone-9, which led only to anthraquinone formation.[17] A number of variations were investigated, but with little success. Benzene and toluene were tried as solvents, the reaction was conducted both with ice cooling and at the reflux temperature, lithium methyl was used, the Grignard reaction was carried out inversely, and the ester rather than the free acid was submitted to condensation. The difficulty probably is associated with the marked tendency of the anthrone to enolize, and the situation is not without analogy. While a number of Grignard reagents are known to react additively with anthrone in tolerable yield,[18] 2-methylanthrone-9 was found by Barnett and Goodway[19] to react poorly with alkyl Grignard reagents and to give satisfactory results only with benzylmagnesium halides.

Although tests for the possible carcinogenicity of the new benzpyrene derivatives which are being carried out by Drs. Shields Warren and C. E. Dunlap have not progressed long enough to permit a report, observations by these investigators concerning certain products of previous syntheses may be summarized. 6-Hydroxy-3,4-benzpyrene has given a single sarcoma in fifty mice injected; it is thus established that the introduction of a hydroxyl group at either the 4′-,[20] 5-,[21] or 6-position results in a complete or almost complete deactivation of the parent carcinogen. The 2′- and 3′-methyl derivatives, administered by injections at a dosage of 2 mg., have given no tumors in seventeen months; these benz-substituted compounds thus appear to be even less potent than the 4′-methyl isomer, our sample of which was found by Shear[22] to give tumors after an average induction period of about 28 weeks.[20] 6-Methyl-3,4-benzpyrene is likewise distinctly less active than the parent hydrocarbon, for it has given sarcomas in only 7 of 20 injected mice in an average time of 23 weeks. The 9-methyl isomer, however, has produced tumors in all of 5 C_3H-mice injected with 1 mg. of material in tricaprylin solution in twelve weeks (average), and this appears to be at least as potent a carcinogen as the parent hydrocarbon, which produces tumors in mice of highly or moderately susceptible strains in 12 to 15 weeks.[20,23] From the report by Shear and Leiter,[21] it appears that our 5-methyl-1,2-benzpyrene is roughly comparable in activity with the 9-isomer.

Acknowledgment is made to the Jane Coffin Childs Fund for Medical Research for a generous grant in support of the biological experimentation.

Experimental Part[24]

4-(γ-Carboxypropyl)-benzophenone-2′-carboxylic Acid (I).—Yellow commercial aluminum chloride (115 g.) was finely ground and allowed to stand for two hours in an open 250-cc. Erlenmeyer flask with occasional shaking. The material was then added gradually in the course of twenty-five minutes to a stirred and ice-cooled mixture of 41 g. of γ-phenylbutyric acid and 37 g. of pulverized phthalic anhydride in 500 cc. of purified tetrachloroethane, contained in a 1-liter three-necked flask. Hydrogen chloride was evolved and a practically clear solution resulted and gradually changed in color from yellow-green to red-brown. After one hour and twenty minutes the flask was removed from the ice-bath but stirring was continued, and within a further period of forty-five minutes a considerable amount of a raspberry colored complex rapidly separated from the solution. The tendency of the precipitate to coagulate to a tough mass was prevented by inserting a stationary baffle rod through a side opening of the flask in a slanted position into the stirred mixture. The slow evolution of gas ceased about eight and one-half hours after the addition of the aluminum chloride, but stirring was continued overnight. The complex was then collected on a suction filter, washed with a little solvent, and added in portions to 1 liter of ice water containing enough hydrochloric acid to keep the aluminum in solution. Adhering solvent was removed by steam distillation; when the mixture had cooled, a part of the product had crystallized from the supernatant liquid and was collected separately, giving 2.75 g. (3.5%) of I, m. p. 144–149°. The bulk of the product remained as a brown cake of solidified oil. This was dissolved in 2 liters of ether and the solution was dried, clarified with Darco, and evaporated, leaving a light yellow oil which crystallized when triturated with ethyl acetate. Crystallization from the same solvent afforded the following crops: 30.4 g. (148–150.5°), 9.55 g. (147–149.5°), 3.3 g. (142–148°); total yield of satisfactory acid, 46.0 g. (58%). Further purification is best accomplished by crystallization from dilute acetic acid; the pure compound forms colorless prisms, m. p. 149.4–151.6°.

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[17] Fieser and Seligman, THIS JOURNAL, **60**, 170 (1938).

[18] Krollpfeiffer and Branscheid, *Ber.*, **56**, 1617 (1923); Sieglitz and Marx, *ibid.*, **56**, 1619 (1923).

[19] Barnett and Goodway, *J. Chem. Soc.*, 1759 (1929).

[20] See Fieser, *Am. J. Cancer*, **34**, 37 (1938).

[21] Shear and Leiter, *J. Natl. Cancer Inst.*, **1**, 303 (1940).

[22] Shear, *Am. J. Cancer*, **36**, 211 (1939).

[23] Shimkin and Andervont, *J. Natl. Inst. Cancer*, **1**, 57 (1940).

[24] All melting points are corrected.

Anal. Calcd. for $C_{18}H_{16}O_5$: C, 69.23; H, 5.16; mol. wt., 312; neut. equiv., 156. Found: C, 69.58[25]; H, 4.85[25]; mol. wt. (Rast), 320; neut. equiv., 154.4, 155.6.

No additional product was found on working up the crystallization mother liquors or the tetrachloroethane filtrate, but steam distillation of the latter solution afforded solvent suitable for subsequent runs. Final variations in the procedure included extending the time, raising the temperature and changing the order of addition.

4-(γ-Carboxypropyl)-diphenylmethane-2′-carboxylic Acid (II). (a).—A solution of 58.8 g. of the once recrystallized keto diacid I in sodium hydroxide (about 200 cc.) was adjusted to neutrality with a little hydrochloric acid and placed with 10 g. of copper chromite catalyst (KAF-37) in a copper bomb liner. At 200° and an initial pressure of 3000 lb., two moles of hydrogen was consumed in the course of five hours. The solution was boiled with a little sodium carbonate to precipitate any barium derived from the catalyst, filtered, and acidified while still hot. The product separated in an oily, hydrated condition but became granular on digestion at the boiling point, giving 50.6 g. (90.5%) of II, m. p. 139.6–141°. The substance crystallizes well from acetic acid–water, from which it separates either in the form of needles or as hexagonal plates. The needle-form when heated rapidly sintered at about 134–136°; when heated slowly from 115° this initial sintering is not observed and the melting point is the same as that of the plate-form, m. p. 141.2–142.4°.

Anal.[25] Calcd. for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.78; H, 6.03.

(b). The advantages in the use of the sodium salt for the hydrogenation are illustrated by the results of the following comparison experiment. A mixture of 3 g. of the keto diacid and 0.75 g. of copper chromite catalyst in 7 cc. of dioxane was hydrogenated at 170° and 2400 lb. initial pressure (six hours). The resulting solution was deep green and could not be filtered; it was diluted with water and the precipitated material was taken up in soda solution. The solution was filtered from catalyst and residue (green) and the still colored filtrate acidified. The green color persisted on crystallization from dilute acetic acid, which afforded 2.03 g. (71%) of II, m. p. 136.4–140.8°.

2-(γ-Carboxypropyl)-anthrone-9 (III).—A solution of 10 g. of II in 180 g. of liquid hydrogen fluoride was allowed to stand at room temperature for forty-five minutes and poured into 1250 g. of ice water. The precipitate was coagulated by stirring, collected, stirred with 1.5 l. of water and collected. On treatment with ether, the product proved to be but sparingly soluble, and the solvent was therefore filtered and evaporated, giving 1.7 g. of the anthrone, m. p. 145.7–147°. The bulk of the product was dried and dissolved in 200 cc. of hot benzene, and after clarification with Darco there was obtained 4.55 g. of slightly yellowish needles, m. p. 145–147°; total yield 66.5%. The fully purified material was very faintly cream colored and melted at 145.4–146.8°.

Anal.[25] Calcd. for $C_{18}H_{16}O_3$: C, 77.13; H, 5.75. Found: C, 77.36; H, 5.76.

Crystallization of the crude, moist product of cyclization from acetone gave satisfactory material in some instances, but more often the product was decidedly yellow and sintered at about 142° before melting. Thus in a typical 5-g. run there was obtained 3.2 g. (70%) of anthrone melting at 145–147° with previous softening, and 0.33 g. (7%), m. p. 140–145°.

For the preparation of the **methyl ester of III,** 10 g. of the diphenylmethane diacid II was first treated with excess diazomethane in ethereal solution. Evaporation of the solvent left an oil, and this was treated with 200 g. of hydrogen fluoride for forty-five minutes and the solution poured into 1.5 liters of ice water. The semisolid material which precipitated was taken into ether and the solution was washed, dried, clarified, concentrated to about 50 cc., and diluted with petroleum ether to the point of permanent turbidity. The anthrone ester soon crystallized in the form of nearly colorless, thin needles, m. p. 74–75.4°; yield 6.05 g. (61%). The compound can be recrystallized from either hexane or methanol, but prolonged boiling in the latter solvent leads to decomposition. The best sample consisted of fine, faintly cream-colored needles, m. p. 75.8–77.8°. The same ester resulted from the treatment of III with diazomethane.

Anal. Calcd. for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.34; H, 6.21.

γ-(2-Anthryl)-butyric Acid[6] (IV).—The crude precipitated and washed anthrone obtained by treatment of 15 g. of the diacid II with hydrogen fluoride for twenty minutes was mixed with 30 g. of zinc dust (activated with copper sulfate), 210 g. of 29% ammonium hydroxide, and 200 cc. of water, when a yellow-brown solution resulted. After heating on the steam-bath for about four hours the color had changed to light yellow. The supernatant liquor was filtered from a residue containing zinc and this was digested with hydrochloric acid until the zinc had been destroyed. The undissolved residue was combined with the gelatinous material which resulted on acidification of the ammoniacal filtrate. The dried product was taken up in 700 cc. of toluene and the filtered solution was treated with Darco and allowed to cool; the only faintly colored crystallizate consisted of 9.5 g. (72%) of the anthrylbutyric acid, m. p. 196.6–198.5°. It is advisable to use the large volume of toluene specified, for otherwise considerable material is retained by the clarifying agent. In spite of the high dilution, practically all of the product is recovered on cooling, for only traces of the acid can be obtained on concentration of the mother liquor. One recrystallization from acetic acid gave colorless, blue-fluorescent leaflets melting at 196.5–198.5° and giving no depression when mixed with an authentic sample[6] of the acid.

The yield cited was reproduced in several experiments but in one case was only 65.5% (19.4 g. of starting material).

1′-Keto-1′,2′,3′,4′-tetrahydro-1,2-benzanthracene[6] (V).—A mixture of 3 g. of the anthrylbutyric acid and 2.7 g. of phosphorus pentachloride in 50 cc. of dry benzene in a flask equipped with a stirrer, condenser and dropping funnel was heated to boiling for a few minutes, when a clear orange solution resulted. This was cooled in ice, whereupon a tan precipitate separated. With cooling and stirring of the suspension, a solution of 2 cc. of anhydrous stannic chloride in 5 cc. of benzene was added by drops. This produced an immediate purple coloration and the solid went into

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[25] Microanalysis by H. S. Wight.

solution. The ice-bath was removed and stirring was continued at room temperature for thirteen hours; ice water containing 20 cc. of concentrated hydrochloric acid was then added with vigorous stirring, and stirring was continued until the difficultly hydrolyzed purple complex had completely disappeared. The benzene layer was separated, filtered from a trace of suspended solid (which otherwise causes trouble in the subsequent extractions), washed with 2 *N* hydrochloric acid until no tin could be detected in the extracts and then washed with 0.5% soda solution to remove a trace of organic acid. The neutral product recovered from the dried solution was a reddish oil which soon solidified. Crystallization from alcohol afforded 2.25 g. (80.5%) of ketone, m. p. 112–113.5°, and recrystallization raised the melting point to 112.8–114.2° (Cook and Robinson,[5] 114–114.5°). In a subsequent 9-g. run the yield was 6.2 g. (74%).

Cyclization of 1.7 g. of IV with hydrogen fluoride gave in the neutral fraction 1.26 g. (79.5%) of crystalline yellow material melting over the range 109–113°. Samples purified by recrystallization and sublimation or by chromatographic absorption appeared still to be mixtures (m. p. 110–113°).

Methyl 1'-Hydroxy-1',2',3',4'-tetrahydro-1,2-benzanthryl-1'-acetic Ester (VI).—A mixture of 5 g. of the ketone V, 10 g. of zinc granules (arsenic-free, washed with hydrochloric acid, water and acetone and dried at 100°), 2.5 cc. of redistilled methyl bromoacetate, 140 cc. of dry benzene, and 35 cc. of absolute ether was placed in a flask equipped with a stirrer and reflux condenser. A crystal of iodine was added and the mixture was refluxed and stirred. A turbidity was noticed in fifteen minutes, and after fifty-five minutes a granular yellow precipitate suddenly separated. Heating was continued for thirty minutes, and the complex was decomposed by the addition of methanol and then acetic acid, until a clear solution resulted. Extraction with dilute ammonium hydroxide removed some coloring matter, and the dried solution was further clarified with Darco and then evaporated at reduced pressure to an oil. This was dissolved in alcohol and the solution was treated with Darco and concentrated to a volume of 80 cc. The solution on cooling deposited 5.1 g. (78.5%) of large yellow prisms which melted over the range 135–146°, dec. A sample recrystallized four times from alcohol decomposed at about the same temperature (139–148°).

Anal.[26] Calcd. for $C_{21}H_{20}O_3$: C, 78.73; H, 6.29. Found: C, 79.04; H, 6.46.

The yield in this condensation is quite reproducible, although there is considerable variation in the time at which the separation of the complex occurs. In one instance the reaction took three hours, but the yield nevertheless amounted to 78%.

Methyl Dehydro-1',2',3',4'-tetrahydro-1,2-benzanthryl-1'-acetic Ester (VII). (a).—A round-bottom flask containing 4.49 g. of the hydroxy ester VI was evacuated at the water pump and heated until the solid melted. A vigorous gas evolution ensued and lasted about three minutes. The glassy mass was warmed with 100 cc. of alcohol, whereupon it changed to a yellow solid which subsequently dissolved. After treatment with Darco and concentration to a volume of 60 cc. the solution on cooling deposited 2.29 g. (53.5%) of the unsaturated ester in the form of long yellow needles, m. p. 139–144°. Three recrystallizations from alcohol (Darco) yielded a light yellow sample, m. p. 148.4–150.4°.

Anal. Calcd. for $C_{21}H_{18}O_2$: C, 83.42; H, 6.02. Found: C, 83.57; H, 6.10.

(b). A solution of 250 mg. of VI in 5 cc. of pyridine was treated with 0.5 cc. of phosphorus oxychloride and refluxed for about fifteen minutes. The brownish solution was poured slowly into 200 cc. of ice water and 5 cc. of concentrated hydrochloric acid and the precipitated product was taken up in ether and the solution was washed, dried and evaporated. Purification of the residue from alcohol gave 110 mg. (47%) of VII, m. p. 140–145°.

(c). A solution of 100 mg. of VI in 5 cc. of 77% formic acid was boiled for three minutes, when the color changed from red to yellow and the solution became cloudy. The product was collected in ether and crystallized from alcohol giving 55 mg. (57%) of VII in the form of brownish needles, m. p. 146–148°.

Dehydro-1',2',3',4'-tetrahydro-1,2-benzanthryl-1'-acetic Acid.—The free acid was obtained in a trial of a fourth method of dehydration. A suspension of 1 g. of VI in a mixture of 10 cc. of benzene, 0.88 cc. of pure thionyl chloride, and 0.44 cc. of pyridine was warmed briefly in a bath at 40°, when an oil settled out. After shaking the suspension for fifteen minutes it was drowned in ice water and the benzene layer was separated, combined with a benzene extract of the aqueous layer, washed, and treated with 50 cc. of alcohol containing 2 g. of potassium hydroxide. The mixture was refluxed for one and one-half hours and poured into water, and the aqueous layer was separated, boiled until free of organic solvents, clarified with Norit at the neutral point, and acidified. Crystallization of the precipitated material from aqueous acetic acid afforded 280 mg. (31%) of the unsaturated acid in the form of yellow needles, dec. 238°. Three further crystallizations gave large hexagonal needles which decomposed violently at 241–245°.

Anal. Calcd. for $C_{20}H_{16}O_2$: C, 83.31; H, 5.59. Found: C, 83.45; H, 5.85.

1,2-Benzanthryl-1'-acetic Acid (IX) and 1',2',3',4'-Tetrahydro-1,2-benzanthryl-1'-acetic Acid (VIII). (a). From the Hydroxy Ester.—This reaction as well as the other dehydrogenations reported below, was carried out in a boiling tube specially designed for application of the Linstead technique to small-scale operations.[27] This consists of a 3.5 × 24-cm. tube fitted with a ground-glass cold finger condenser extending to within 4–5 cm. of the bottom of the tube and provided with a gas inlet tube sealed into the side wall 8–10 cm. from the bottom and an outlet tube just below the joint. The tube was charged with 2 g. of VI, 200 mg. of platinized charcoal-d,[28] and 10 cc. of α-methylnaphthalene which had been refluxed and distilled over sodium. Pure carbon dioxide from a Kipp generator was passed through the system and into a 100-cc. azotometer filled with 50% potassium hydroxide solution until microbubbles were obtained. The reaction mixture was then boiled

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[26] Microanalysis by Lyon Southworth.

[27] See Fig. 79, Fieser, "Experiments in Organic Chemistry," 2nd edition, D. C. Heath and Co., Boston, Mass., 1941, p. 462.

[28] Linstead and Thomas, *J. Chem. Soc.*, 1127 (1940).

vigorously, while steam, rather than water, was being passed through the condenser, and with maintenance of a slow current of carbon dioxide. After fifty-three minutes, by which time 40.5 cc. of gas had collected in the azotometer, the rate of gas evolution dropped abruptly and the volume increase during the next hour amounted to only 1.9 cc. The total evolution of hydrogen at standard conditions was 38.5 cc. (0.285 molecular equivalent).

The reaction mixture was filtered from catalyst, which was washed with absolute alcohol, and treated with a solution of 5 g. of potassium hydroxide in absolute alcohol and with enough of this solvent to make up the volume to 100 cc. The mixture was then refluxed for one hour and poured into 700 cc. of water, and the methylnaphthalene and other non-acidic material (fluorescence) was removed by extraction with ether. The alkaline solution was boiled to remove organic solvents, treated with Norit, acidified. A solution of the dried precipitate in 30 cc. of benzene was clarified with Darco and diluted with ligroin (70–90°) until crystallization commenced, and on cooling there separated 725 mg. (40.5%) of **1,2-benzanthryl-1′-acetic acid** in the form of white needles, m. p. 200–204.5°. A sample fully purified by crystallization from benzene–ligroin melted at 203.6–204.6°.

Anal. Calcd. for $C_{20}H_{14}O_2$: C, 83.90; H, 4.93. Found: C, 83.79; H, 5.04.

The first benzene–ligroin mother liquor was evaporated to dryness and the residue was dissolved in ethanol. Water was added at the boiling point until the solution was saturated, and the solution on cooling deposited 470 mg. (26%) of **1′,2′,3′,4′-tetrahydro-1,2-benzanthryl-1′-acetic acid,** m. p. 206–209°. After further purification, the substance formed colorless leaflets, m. p. 209.4–211.4° with slight previous softening.

Anal. Calcd. for $C_{20}H_{18}O_2$: C, 82.73; H, 6.25. Found: C, 82.64, 82.78; H, 6.34, 6.18.

The methyl ester, prepared with the use of diazomethane, was distilled at 150° at 1 mm. and crystallized from methanol (cooled in ice–salt bath); it forms small, faintly yellow prisms, m. p. 77–78.8°, and is very soluble in the usual organic solvents.

Anal. Calcd. for $C_{21}H_{20}O_2$: C, 82.86; H, 6.62. Found: C, 82.82; H, 6.62.

(b). From the Unsaturated Ester VII.—The dehydrogenation of 900 mg. of VII, conducted by the procedure described above, afforded 430 mg. (50.5%) of IX, m. p. 200–204°, and 140 mg. (15.5%) of the tetrahydride VIII, m. p. 205.5–210°.

(c). From VII by Hydrogenation and Dehydrogenation.—A solution of 1.81 g. of the unsaturated ester VII (m. p. 147–150°) in 100 cc. of pure ethyl acetate was shaken with hydrogen in the presence of 200 mg. of Adams catalyst. Absorption of hydrogen stopped after twenty-nine hours, when the gas consumption (252 cc.) was very close to the theoretical amount calculated for two moles (261 cc.). Evaporation of the filtered solution at reduced pressure left an oil, which was dissolved in 10 cc. of α-methylnaphthalene and boiled with 200 mg. of platinized charcoal-d. In the course of six and three-quarters hours, a total of 170 cc. of gas had collected in the azotometer (not corrected for possible inert gas in the carbon dioxide). The reaction mixture was worked up as in (a) and on seeding the dilute alcoholic solution of the acidic portion there was isolated 400 mg. (24%) of 1′,2′,3′,4′-tetrahydro-1,2-benzanthryl-1′-acetic acid, in the form of slightly brownish leaflets, m. p. 195–200°.

2-Hydroxy-3,4-benzpyrene (XII).—A solution of 1.2 g. of 1,2-benzanthryl-1′-acetic acid in 50 cc. of hydrogen fluoride was allowed to stand for one-half hour and drowned in 1 liter of water. The precipitated material, which changed from an initial brownish color to yellow, was extracted with two 75-cc. portions of ether. When washed with water and bicarbonate solution and clarified with Darco, the ethereal solution was light yellow and fluorescent. The recovered material when recrystallized from benzene afforded a total of 890 mg. (79%) of the hydroxy compound in two crops. The mother liquors darken rapidly on standing but, since the colored impurity is effectively removed by treatment with Darco, the pure hydroxy compound present can be isolated without difficulty. One recrystallization of the material from benzene gave 760 mg. of shiny yellow leaflets which decompose at 220°.

Anal. Calcd. for $C_{20}H_{12}O$: C, 89.53; H, 4.59. Found: C, 89.37; H, 4.58.

The acetate, prepared by warming a mixture of 100 mg. of XII and 2.5 cc. of acetic anhydride and 2.5 cc. of pyridine for one-half hour on the steam-bath, crystallized from alcohol (40 cc.) in pale yellow, feathery crystals, m. p. 189.6–190.9°.

Anal. Calcd. for $C_{22}H_{14}O_2$: C, 85.14; H, 4.54. Found: C, 84.72, 85.05; H, 4.70, 4.65.

2-Keto-1,2,8,9,10,10a-hexahydro-3,4-benzpyrene (X).—A solution of 60 mg. of the tetrahydro acid VIII (m. p. 209.4–211.4°) in 20 g. of hydrogen fluoride was poured into water after one hour and the product extracted with ether. The collected product was crystallized twice from alcohol and gave 33 mg. of the pure ketone in the form of small yellow needles, m. p. 139.2–141.4°. From the mother liquors there was obtained 6.5 mg. of material, m. p. 137–141°; total yield 70%.

Anal. Calcd. for $C_{20}H_{16}O$: C, 88.20; H, 5.92. Found: C, 88.44; H, 6.12.

2-Methyl-3,4-benzpyrene (XI).—A total of 630 mg. of the tetrahydro acid VIII (two lots, m. p. 195–200° and 209–211°) was cyclized as above, giving 530 mg. (90%) of crude ketone, m. p. 123–133° (a recrystallized sample melted at 135–137.5°). An ethereal solution of 500 mg. of the crude ketone was added to the methylmagnesium bromide solution from 82 mg. of magnesium. An orange precipitate soon formed, and the suspension was stirred overnight and decomposed with dilute hydrochloric acid. The reaction product was an orange oil which failed to crystallize. It was dissolved in 6 cc. of α-methylnaphthalene and boiled with 100 mg. of platinized charcoal-d. The gas evolution slackened after thirty-five minutes, when 60 cc. of gas had been collected (72% of the theoretical amount). After filtration of the catalyst and removal of the solvent in vacuum, a brownish yellow solid was obtained. A benzene solution of the product was passed through a tower of activated alumina and the column was eluted with benzene until all fluorescent material had been removed. On evaporation of the light yellow filtrate to a volume of 5 cc., thin yellow blades of the hydrocarbon crystallized. The substance melted at 161.4–162.4° when heated slowly, but when immersed in a bath at 158° it melted immediately. Two recrystallizations from hexane gave 60 mg. of light yellow leaflets which melted at 165–167°, and remelted at 168–168.8°. A second crop of 26 mg. melted initially at 164–166.2° and then at 167.4–168°. The material from a portion of the mother liquors was separated as the crude picrate (m. p. 180–183°) and the hydrocarbon was recovered, sublimed at 135° and 1 mm., and crystallized from hexane, giving 18 mg. of satisfactory material (final m. p. 167.4–168.4°); total yield, 21%. A mixture of this substance with 3,4-benzpyrene (m. p. 178.5–179°) melted initially at 144–159°.

Anal. Calcd. for $C_{21}H_{14}$: C, 94.70; H, 5.30. Found: C, 94.63, 94.76; H, 5.63, 5.52.

The picrate crystallized from benzene–ethanol in the form of black needles, m. p. 187.6–188.5°.

Anal.[29] Calcd. for $C_{27}H_{17}O_7N_3$: C, 65.35; H, 3.46. Found: C, 65.96, 65.89; H, 3.58, 3.30.

γ-(9-Methylanthryl-2)-butyric Acid (XIII). (a).—To the methylmagnesium chloride solution from 0.75 g. of magnesium was added 3 g. of 2-(γ-carboxypropyl)-anthrone-9 and 200 cc. of dry benzene. After the suspension had been stirred at room temperature for a short time, the starting material gave place to a yellow precipitate. After six hours the ether was removed by distillation and the resulting benzene solution was refluxed for one-half hour and then decomposed with dilute acid. The washed organic layer was extracted with sodium carbonate solution and the extract treated with saturated sodium chloride solution, which precipitated a brown oil. After decantation of the supernatant liquor, this was dissolved in 750 cc. of water and the solution acidified. The precipitated material was a sticky brown mass, but crystallization from acetic acid afforded 0.5 g. (17%) of the methylated product XIII, m. p. 150–151°. The acid was purified further through its nicely crystalline sodium salt and by crystallization from benzene–hexane. It formed yellow blades, m. p. 151.4–153°.

Anal.[25] Calcd. for $C_{19}H_{18}O_2$: C, 81.99; H, 6.51. Found: C, 81.89; H, 6.39.

(b).—An ethereal solution of 1 g. of the methyl ester of III was added to a methylmagnesium iodide solution from 83 mg. of metal and the resulting suspension containing a yellow precipitate was refluxed for a short time and treated with acid. The collected oily reaction product was refluxed for five hours with 175 cc. of 0.25% aqueous sodium hydroxide, and the resulting cloudy yellow solution was filtered and concentrated to a volume of 50 cc. The solution on cooling deposited a bright red precipitate, and acidification of an aqueous solution of this material gave 0.4 g. of crude product which proved to be a mixture. A solution of the material in dilute acetic acid was allowed to cool until a first crop of crystals had separated, and the mother liquor was decanted while still warm. The crystallizate consisted of 100 mg. (10.6%) of XIII, m. p. 149–151°. The mother liquor on thorough cooling deposited an amorphous yellow solid, which when crystallized repeatedly from benzene–toluene and finally from methanol, afforded pale yellow needles of **γ-(anthraquinonyl-2)-butyric acid,** m. p. 177.6–178.2° (red vat test).

Anal.[26] Calcd. for $C_{18}H_{14}O_4$: C, 73.46; H, 4.79. Found: C, 73.29; H, 4.83.

In another experiment, 1 g. of the methyl ester of the anthrone acid III was treated with methyllithium in ethereal solution. From the oily material resulting on working up the reaction mixture there was obtained a crystallizate consisting of 200 mg. (19%) of **methyl γ-(9-methylanthraquinonyl-2)-butyric acid.** Four recrystallizations afforded slender, faintly yellow needles, m. p. 108.2–109.2°.

Anal.[26] Calcd. for $C_{19}H_{16}O_4$: C, 74.02; H, 5.23. Found: C, 74.20; H, 5.24.

Summary

The synthesis of 2-hydroxy and 2-methyl-3,4-benzpyrene has been accomplished via the hydroxy ester resulting from the Reformatsky reaction of methyl bromoacetate with 1′-keto-1′,2′,3′,4′-tetrahydro-1,2-benzpyrene. This ketone was prepared by a new synthesis starting with the Friedel and Crafts condensation of phthalic anhydride with γ-phenylbutyric acid.

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(29) Microanalyses by the Arlington Laboratories and Eleanor Werble.