[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF NEW MEXICO]

The Synthesis of 2-Methyl-3,4-benzpyrene and 2,8-Dimethyl-3,4-benzpyrene[1,2]

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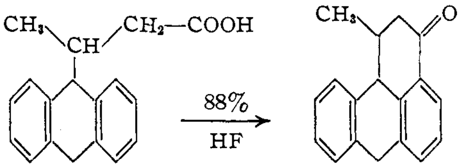
The Michael condensation of anthrone (I) with ethyl crotonate followed by reduction gave β-(9,10-dihydro-9-anthranyl)-butyric acid (II), which was cyclized to give 1-methyl-3-keto-1,2,3-11b-tetrahydro-7H-*meso*benzanthracene (III). The Stobbe condensation with this ketone gave a mixture of half-esters, which when decarbethoxylated gave β-(1-methyl-1,11b-dihydro-7H-*meso*benzanthrenyl)-3-propionic acid (V). Reduction of V gave β-(1-methyl-1,2,3,11b-tetrahydro-7H-*meso*-benzanthrenyl-3)-propionic acid (VI), and cyclization of this acid gave the ketone VIII which was reduced by the Meerwein, Ponndorf and Verley method or methylated with methylmagnesium iodide producing carbinols which were dehydrated and dehydrogenated to 2-methyl-3,4-benzpyrene (IX) and 2,8-dimethyl-3,4-benzpyrene (X), respectively. The over-all yield of each hydrocarbon from anthrone was approximately 6 and 7%, respectively. Samples of these hydrocarbons are being evaluated for carcinogenic activity at the Northwestern University Medical School, Evanston, Ill.

Ten of the possible twelve monomethyl-3,4-benzpyrenes have been reported previously, namely, the 1′-,[4a,b] 2′-,[4a,c] 3′-,[4a,c] 4′-,[4d] 2-,[4e] 5-,[4f] 6-,[4b] 8-,[4g] 9-[4h] and 10-.[4i]

This paper reports a new synthesis of 2-methyl-3,4-benzpyrene (IX) and the synthesis of a third dimethyl derivative, 2,8-dimethyl-3,4-benzpyrene (X), from anthrone (I). Anthrone was converted to β-(9,10-dihydro-9-anthranyl)-butyric acid (II) in 40% yield in a manner similar to a procedure described by Daub and Doyle.[5]

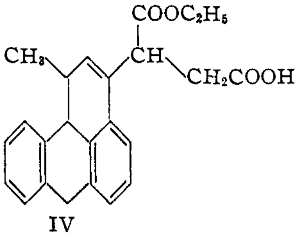
The acid II was cyclized with anhydrous hydrogen fluoride to 1-methyl-3-keto-1,2,3,11b-tetrahydro-7H-*meso*benzanthracene (III) in 88% yield.



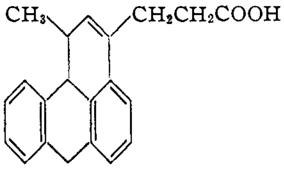
II III

The ketone III was unreactive in the usual Stobbe condensation with diethyl succinate so that a modified procedure based upon Johnson's[6] procedure for unreactive ketones was used giving a mixture of oily half-esters IV. Decarbethoxylation of the crude half-ester mixture gave a crystalline product, β-(1-methyl-1,11b-dihydro-7H-*meso*-benzanthrenyl-3)-propionic acid (V), in an over-all yield of 53% from the ketone III. The double bond in the acid V was shown to be endocyclic by oxidation with potassium permanganate, from which α-(1-succinoyl-9,10-dihydro-9-anthranyl)-propionic acid (VI) was isolated.

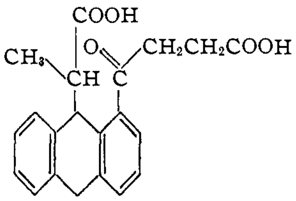
The unsaturated acid V was hydrogenated over Adams catalyst at atmospheric pressure to β-(1-methyl-1,2,3,11b-tetrahydro-7H-*meso*benzanthrenyl-3)-propionic acid (VII) in 79% yield. Cyclization of the acid VII with anhydrous hydrogen fluoride produced the ketone, 2-methyl-8-keto-1,2,2a,5,8,9,10,10a-octahydro-3,4-benzpyrene (VIII), in 89% yield.



IV

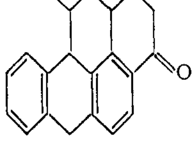


V

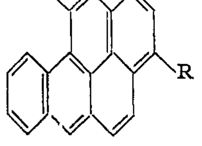


VI

Reduction of the ketone VIII with aluminum isopropoxide in isopropyl alcohol followed by dehydration and dehydrogenation over palladium–charcoal at 320° gave 2-methyl-3,4-benzpyrene (IX) in 48% yield. The hydrocarbon proved to have the same properties as the hydrocarbon reported by Fieser.[4e] Reaction of VIII with methylmagnesium iodide followed by dehydration and dehydrogenation over palladium–charcoal at 320° gave 2,8-dimethyl-3,4-benzpyrene (X) in 56% yield.



VIII



IX, R = H
X, R = CH_3

The ultraviolet absorption spectrum of 2,8-dimethyl-3,4-benzpyrene (X) was similar to those of 2-methyl-3,4-benzpyrene (IX) and 3,4-benz-

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[3] Graduate Research Assistant supported by a grant from the Research Corporation, February, 1951, to February, 1952.

[4] (a) W. E. Bachmann and M. Carmack, THIS JOURNAL, **63**, 2494 (1941); (b) G. A. R. Kon and E. M. F. Roe, *J. Chem. Soc.*, 143 (1945); (c) L. F. Fieser and E. B. Hershberg, THIS JOURNAL, **60**, 1658 (1938); (d) L. F. Fieser and M. Fieser, *ibid.*, **57**, 782 (1935); (e) L. F. Fieser and H. Heymann, *ibid.*, **63**, 2333 (1941); (f) L. F. Fieser and E. B. Hershberg, *ibid.*, **60**, 2542 (1938); (g) J. M. L. Cameron, J. W. Cook and R. Schoental, *J. Chem. Soc.*, 257 (1952); (h) L. F. Fieser and F. C. Novello, THIS JOURNAL, **62**, 1855 (1940); (i) J. L. Adelfang and G. H. Daub, *ibid.*, **77**, 3297 (1955).

[5] G. H. Daub and W. C. Doyle, *ibid.*, **74**, 4449 (1952).

[6] W. S. Johnson, V. L. Stromberg and J. Petersen, *ibid.*, **71**, 1385 (1949).

pyrene[7] verifying the presence of the parent ring system in the new hydrocarbon.

Samples of these hydrocarbons are being tested for carcinogenic activity at Northwestern University Medical School under the direction of Dr. D. Warren Stanger, and preliminary results show both compounds to be more active than 3,4-benzpyrene itself.

Experimental[8]

The Michael Condensation of Ethyl Crotonate with Anthrone (I).—A 3-l. three-necked flask with ground glass joints was fitted with a dropping funnel, condenser and a rubber sleeve sealed stirrer. The air in the system was replaced with dry nitrogen, and 550 ml. of anhydrous *t*-butyl alcohol was added. After 13.9 g. (0.356 g. atom) of potassium was dissolved in the alcohol, 55.5 g. (0.286 mole) of anthrone,[9] m.p. 154–156°, was added with the aid of 10–15 ml. of anhydrous *t*-butyl alcohol. The mixture was heated with stirring on the steam-bath for 30 minutes to aid solution of the anthrone. To this refluxing reddish colored solution was added 45.8 g. (0.401 mole) of ethyl crotonate,[10] b.p. 129–132° at 640 mm., in 50 ml. of anhydrous *t*-butyl alcohol over a period of 1 hr. and 20 minutes. The reaction mixture was acidified with 40 ml. of concentrated hydrochloric acid in 300 ml. of water and approximately 650–700 ml. of aqueous *t*-butyl alcohol was removed by distillation. The ester formed a semi-solid when allowed to cool and the remainder of the solvent was removed with the aid of a sintered glass filter stick. Six hundred milliliters of concentrated hydrochloric acid was added and the solution refluxed for 12 hr. The hydrochloric acid was removed with the aid of a sintered glass filter stick and 120 g. (1.85 g. atoms) of zinc dust (activated with 1.5 g. of copper sulfate), 1080 ml. of concentrated ammonium hydroxide and 720 ml. of water were added and the mixture refluxed on a steam-bath for 12 hr. The pale yellow solution was filtered while hot to remove the zinc dust, allowed to cool and acidified to congo red paper with concentrated hydrochloric acid. The solid acid (almost white) was filtered, washed and dried in the air to give 40.2 g. of acid, m.p. 130–136°, with gas evolution. Purification of the acid, probably β-(9-anthranyl)-butyric acid, proved fruitless although crystallization with ethyl acetate improved the melting point somewhat (m.p. 138–140°).

β-(9,10-Dihydro-9-anthranyl)-butyric Acid (II).—To a refluxing solution of 40.50 g. (0.153 mole) of the crude acid from above in 970 ml. of *n*-amyl alcohol (Eastman Kodak Co. practical grade), in a 2-l. round bottom flask fitted with a reflux condenser, was added 32.8 g. (1.43 g. atoms) of sodium in small pieces over a period of 1.75 hr. The *n*-amyl alcohol was then removed by steam distillation and the oily sodium salt which separated was filtered on glass wool, dissolved in hot water and acidified to congo red with concentrated hydrochloric acid. The gummy acid was recrystallized from ethyl acetate; first crop 26.05 g., m.p. 137–139°; second crop 4.42 g., m.p. 136–139°; third crop 0.26 g., m.p. 133–135°; over-all yield of 40% from I. Further crystallizations from ethyl acetate gave **β-(9,10-dihydro-9-anthranyl)-butyric acid** (II) as small colorless crystals, m.p. 138.5–139.5°.

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81; neut. equiv., 266.3. Found: C, 81.11; H, 6.68; neut. equiv., 264.0.

1-Methyl-3-keto-1,2,3,11b-tetrahydro-7H-mesobenzanthracene (III).—A solution of 28.20 g. (0.106 mole) of β-(9,10-dihydro-9-anthranyl)-butyric acid (II), m.p. 137–139°, in 200 ml. of anhydrous hydrogen fluoride was allowed to stand at room temperature for 3 hr. in a polyethylene beaker, during which time the hydrogen fluoride evaporated to a volume of approximately 50 ml. The red-brown solution was poured on 150 g. of ice to give a yellow semi-solid which was taken up in benzene, washed with water and extracted with 10% sodium carbonate solution. Acidification of the carbonate extracts gave 5.31 g. of recovered acid, m.p. 133–136°. The benzene solution was dried over anhydrous potassium carbonate, concentrated and passed through a short column of alumina (Merck and Co., Inc.). The benzene was evaporated and the residue was crystallized from alcohol, giving as a first crop 18.35 g. of yellow prisms, m.p. 122–123°. A second crop of 0.48 g., m.p. 118–120°, made the total yield 88% based on acid used. Further crystallization from alcohol afforded an analytical sample of **1-methyl-3-keto-1,2,3,11b-tetrahydro-7H-*meso*-benzanthracene** (III) as yellow prisms, m.p. 123–124.5°.

Anal. Calcd. for $C_{18}H_{16}O$: C, 87.06; H, 6.50. Found: C, 87.31; H, 6.46.

The oxime was prepared by refluxing a solution of 0.5 g. of ketone, m.p. 122–123°, and 0.5 g. of hydroxylamine hydrochloride in 10 ml. of alcohol with 0.5 ml. of pyridine for 1.5 hr. To this solution 10 ml. of water was added and a yellow solid separated. This was recrystallized several times from alcohol giving an analytical sample of the oxime as yellow prisms, m.p. 196–197.5°.

Anal. Calcd. for $C_{18}H_{17}NO$: C, 82.10; H, 6.51. Found: C, 82.14; H, 6.70.

The Stobbe Condensation with 1-Methyl-3-keto-1,2,3,11b-tetrahydro-7H-mesobenzanthracene (III).—A solution of 4.96 g. (0.020 mole) of the ketone III, m.p. 122–123°, in 10 ml. of anhydrous *t*-butyl alcohol was placed in a 250-ml. three-necked flask with ground glass joints fitted with a dropping funnel, condenser and a rubber sleeve sealed stirrer. To the refluxing solution in a dry nitrogen atmosphere was added, over a period of 1 hr., a solution of 3.60 g. (0.092 g. atom) of potassium in 80 ml. of anhydrous *t*-butyl alcohol and 16.20 g. (0.093 mole) of diethyl succinate, b.p. 109–112° at 23 mm. The solution was then refluxed for 2.5 hr., cooled and acidified to congo red with 9.2 ml. of concentrated hydrochloric acid in 50 ml. of water, and the *t*-butyl alcohol was removed under reduced pressure. The resulting tan oil was taken up in ether and extracted with 1 *N* ammonium hydroxide. The extracts were washed with ether and acidified to congo red with concentrated hydrochloric acid. The yellow half-ester thus obtained was dissolved in ether and dried over anhydrous magnesium sulfate. The ether was removed under reduced pressure giving 8.40 g. of oily half-ester IV probably containing some unremoved solvent. All attempts to crystallize the product failed and the crude material was used in the next step.

β-(1-Methyl-1,11b-dihydro-7H-*meso*benzanthrenyl-3)-propionic Acid (V).—The oily mixture of half-esters from above was refluxed for a period of 14 hr. in a nitrogen atmosphere with 40 ml. of glacial acetic acid, 20 ml. of concentrated hydrochloric acid and 30 ml. of water. This was cooled and the aqueous phase decanted leaving a yellow semi-solid on the bottom of the flask. Trituration with approximately 50 ml. of ether gave 4.01 g. of acid V, m.p. 150–160° (66% crude yield from the ketone III). Recrystallization from ethyl acetate gave 2.37 g. of yellow prisms, m.p. 161–163.5°. An additional 0.87 g. of acid, m.p. 156–161°, was obtained as a second crop to give a total yield of 53% of crystallized material. Repeated recrystallizations from ethyl acetate gave an analytical sample of **β-(1-methyl-1,11b-dihydro-7H-*meso*benzanthrenyl-3)-propionic acid** (V), m.p. 163–164.5°.

Anal. Calcd. for $C_{21}H_{20}O_2$: C, 82.87; H, 6.62; neut. equiv., 304.4. Found: C, 83.14; H, 6.52; neut. equiv., 302.0.

Ultraviolet Absorption Spectrum.—The ultraviolet absorption spectrum of β-(1-methyl-1,11b-dihydro-7H-*meso*-benzanthrenyl-3)-propionic acid (V) in 95% ethanol was measured with a model DU Beckman spectrophotometer. The maximum and (log ϵ) values are 266 $m\mu$ (3.94).[11]

Oxidation of β-(1-Methyl-1,11b-dihydro-7H-mesobenzanthrenyl-3)-propionic Acid (V).—A solution of 1.00 g. (0.0033 mole) of the unsaturated acid V, m.p. 160–163.5°, in 5 ml. of 1 *N* sodium hydroxide and 100 ml. of water was covered with 30 ml. of benzene, chilled in an ice-bath, and 150 ml. of a 0.67% solution of potassium permanganate was added dropwise with stirring over a period of 35 minutes. The solution was then made acid to congo red, the manganese dioxide removed by filtration and this washed with an additional 30 ml. of benzene. The benzene phase was extracted with 10% sodium carbonate which when acidified gave a

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[7] R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Aromatic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1951, pp. 554 and 555.

[8] All melting points are uncorrected.

[9] K. H. Meyer, "Organic Syntheses," Coll. Vol. 1, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 60.

[10] D. A. Shirley, "Preparation of Organic Intermediates," John Wiley and Sons, Inc., New York, N. Y., 1951, p. 148.

small amount of dark, gummy acid. The benzene phase was dried over anhydrous magnesium sulfate and evaporated to give 0.10 g. of material, m.p. 137–150°. This was acidic material due to incomplete extraction with the sodium carbonate. This was crystallized from benzene and recrystallized from ethyl acetate to give a few milligrams of α-(1-**succinoyl-9,10-dihydro-9-anthranyl**)-propionic acid (VI), as colorless needles, m.p. 210–211.5°.

Anal. Calcd. for $C_{21}H_{20}O_5$: C, 71.57; H, 5.72. Found: C, 71.58; H, 5.48.

β-(1-Methyl-1,2,3,11b-tetrahydro-7H-*meso*benzanthrenyl-3)-propionic Acid (VII).—A solution of 2.42 g. (0.0079 mole) of the acid VII, m.p. 163–164.5°, in 100 ml. of absolute ethanol was hydrogenated at atmospheric pressure in the presence of 0.10 g. of Adams catalyst. After 20 hr. of stirring at room temperature the solution absorbed approximately 90% of the theoretical volume of hydrogen. The alcoholic solution was filtered and concentrated to give as a first crop, 1.78 g. of the acid VII, m.p. 149–154°; the second crop gave 0.15 g., m.p. 144–149° (79% yield). Several recrystallizations from ethyl acetate afforded colorless **β-(1-methyl-1,2,3,11b-tetrahydro-7H-*meso*benzanthrenyl-3)-propionic acid** (VII), m.p. 155–156°.

Anal. Calcd. for $C_{21}H_{22}O_2$: C, 82.32; H, 7.24; neut. equiv., 306.4. Found: C, 82.56; H, 7.09; neut. equiv., 306.2.

2-Methyl-8-keto-1,2,2a,5,8,9,10,10a-octahydro-3,4-benzpyrene (VIII).—A solution of 2.51 g. (0.0082 mole) of the acid VII, m.p. 150–154°, in 50 ml. of anhydrous hydrogen fluoride was allowed to stand in a polyethylene beaker at room temperature for 2 hr. during which time almost all of the hydrogen fluoride evaporated. Two hundred milliliters of water was added to the cherry-red complex and the yellow semi-solid residue was dissolved in benzene. The benzene solution was washed with water and 10% sodium carbonate solution. Acidification of the carbonate washings yielded only a trace of unreacted acidic material. The benzene solution was concentrated and chromatographed through a short column of alumina (Merck). The benzene was evaporated and the resulting yellow oil dissolved in hot alcohol and allowed to cool. The ketone VIII crystallized in yellow needles; first crop 2.01 g., m.p. 116–117°; second crop 0.10 g., m.p. 112–114° (89% yield). Repeated crystallizations from alcohol gave an analytical sample of **2-methyl-8-keto-1,2,2a,5,8,9,10,10a-octahydro-3,4-benzpyrene** (VIII) as pale yellow needles, m.p. 116–117°.

Anal. Calcd. for $C_{21}H_{20}O$: C, 87.46; H, 6.99. Found: C, 87.68; H, 7.15.

2-Methyl-3,4-benzpyrene (IX).—A solution of 1.80 g. (0.00625 mole) of the ketone VIII, m.p. 116–117°, and 3.00 g. (0.0192 mole) of aluminum isopropoxide in 125 ml. of anhydrous isopropyl alcohol was refluxed using a Hahn condenser so that acetone–isopropyl alcohol distilled over at a rate of about 3 drops per minute. After 12 hr. of refluxing no more acetone was detected in the distillate. Part of the isopropyl alcohol was then removed under reduced pressure and the reaction mixture was hydrolyzed with 20 ml. of concentrated hydrochloric acid in 80 ml. of water. The colorless gummy residue was dissolved in benzene, washed with water and dried over anhydrous magnesium sulfate. The benzene solution of the resulting carbinol was concentrated and the oily residue was heated with 0.18 g. of 10% palladium–charcoal in an apparatus described by Fieser.[11] The system was swept with carbon dioxide and the dehydrogenation apparatus was heated rapidly in an electrically heated aluminum block to a temperature of 320°. Approximately 74% of the theoretical volume of hydrogen was evolved. The solid residue was dissolved in benzene and the catalyst removed by filtration. The yellow benzene solution was chromatographed through a short column of alumina (Merck), concentrated and allowed to crystallize giving 0.98 g., m.p. 161–162.5° (59% yield from the ketone VIII). This was redissolved in benzene, chromatographed and crystallized giving 0.52 g. of glistening yellow plates, m.p. 165–166.5°, remelted at 166.5–167.5°, reported[4e] m.p. 168–168.8°. The mother liquors were chromatographed twice more and the benzene evaporated. The residue was dissolved in 60–90° petroleum ether and allowed to crystallize, giving 0.28 g., m.p. 164.5–167°, for a total of 0.80 g. (48% yield from the ketone VIII).

2,8-Dimethyl-3,4-benzpyrene (X).—In a 200-ml. three-necked flask, with ground glass joints fitted with a condenser, dropping funnel and a rubber sleeve sealed stirrer, was placed 0.50 g. (0.021 g. atom) of magnesium turnings, 1.3 ml. (0.021 mole) of methyl iodide in 60 ml. of absolute ether being added from a dropping funnel over a period of 1.5 hr. To the Grignard solution was added a solution of 1.35 g. (0.0047 mole) of the ketone VIII, m.p. 115–116.5°, in 80 ml. of dry ether over a 15-minute period, a yellow addition product separating at this point. The solution was stirred an additional 30 minutes, and the complex was decomposed by adding 3 ml. of saturated ammonium chloride solution as fast as refluxing would permit. The ether solution was decanted from the precipitated magnesium salts and dried over anhydrous potassium carbonate and concentrated to a yellow oil which was heated rapidly in a dehydrogenation apparatus with 0.13 g. of 10% palladium–charcoal to a temperature of 320° in a carbon dioxide atmosphere. About 67% of the theoretical volume of hydrogen was evolved. The solid residue was dissolved in benzene, filtered and chromatographed through a short column of alumina (Merck) and concentrated to give 0.67 g. of crude X, m.p. 135–138°. This was recrystallized from 5:1 petroleum ether (b.p. 60–90°)-benzene to give 0.35 g. of **2,8-dimethyl-3,4-benzpyrene** as yellow needles, m.p. 140–142°.

Anal. Calcd. for $C_{22}H_{16}$: C, 94.25; H, 5.75. Found: C, 94.61; H, 5.79.

The mother liquors were concentrated, the solvent replaced with benzene and the solution chromatographed. The benzene was concentrated and petroleum ether (60–90°) was added until the ratio was 5:1 petroleum ether–benzene and the solution allowed to crystallize giving 0.14 g., m.p. 138–140°. The mother liquors were treated in the same manner again to give 0.25 g., m.p. 139–140°. This made a total of 0.74 g. of purified material (56% yield from the ketone VIII).

The picrate of 2,8-dimethyl-3,4-benzpyrene was prepared by adding a solution of 0.12 g. (0.00052 mole) of picric acid in 5 ml. of benzene to a solution of 0.14 g. (0.00050 mole) of X, m.p. 138–140°, in 5 ml. of benzene. This was concentrated slightly to give 0.25 g. of the picrate as brown-black needles, m.p. 196–198°. Further recrystallizations failed to change the melting point.

Ultraviolet Absorption Spectrum.—The ultraviolet absorption spectrum of 2,8-dimethyl-3,4-benzpyrene in 95% ethanol was measured with a model DU Beckman spectrophotometer. Maxima and (log ε) values are: 224 mμ (4.40), 265 mμ (4.74), 290 mμ (4.60), 304 mμ (4.70) and 391 mμ (4.33).

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(11) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., 1941, p. 462.