233° (vac.) alone and when mixed with our *dl*-D-homoequilenin (m. p. 232–233°).

Summary

The total synthesis of the *cis* and *trans* forms of four homologs of the sex hormone equilenin is described. These include a homolog containing an angular *n*-propyl group, one with an angular *n*-butyl group, a homolog with a methyl group adjacent to the carbonyl group, and one containing a six-membered D ring.

The results of tests on these compounds for estrogenic activity are reported.

Ann Arbor, Michigan Received July 10, 1941

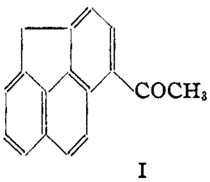
[Contribution from the Chemistry Laboratory of the University of Michigan]

The Synthesis of 1-Methyl-, 1-Ethyl-, and 3-Ethyl-4,5-methylenephenanthrene[1]

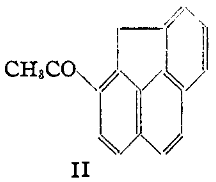
By W. E. Bachmann and John Clark Sheehan[2]

The method which we developed for the synthesis of 4,5-methylenephenanthrene[3] appears to be a general one for the preparation of alkyl derivatives of the hydrocarbon. We have now employed it to prepare 1-ethyl-4,5-methylenephenanthrene (VIII) and 3-ethyl-4,5-methylenephenanthrene (VI) in order to prove the structures of the acetyl compounds formed by acetylation of the parent hydrocarbon.

Fieser and Cason[4] isolated the 1-substituted product from the reaction between 4,5-methylenephenanthrene and succinic anhydride. We have isolated both the 1- (I) and 3-acetyl-4,5-methylenephenanthrene (II) from the acetylation mixture in yields of 30 and 20%, respectively. The structures of the two acetyl derivatives were established by a comparison of the corresponding ethyl derivatives, formed by Clemmensen reduction, with 1- and 3-ethyl-4,5-methylenephenanthrene.



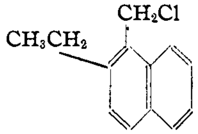
I



II

For the synthesis of 1-ethyl-4,5-methylenephenanthrene, ethylmagnesium bromide was condensed with 1-keto-4,5-methylenetetrahydrophenanthrene (VII), which has been described previously, and the resulting carbinol was dehydrated and dehydrogenated to the hydrocarbon by the action of palladium on charcoal at 280–300°. 1-Methyl-4,5-methylenephenanthrene was prepared in a similar manner by means of methylmagnesium iodide.

For the synthesis of 3-ethyl-4,5-methylenephenanthrene, 2-ethylnaphthalene was condensed with formaldehyde and hydrochloric acid to give 1-chloromethyl-2-ethylnaphthalene (III). The chloride was converted to the nitrile, which was hydrolyzed to 2-ethyl-1-naphthaleneacetic acid (IV). The structure of this acid was established by decarboxylation of its sodium salt to 2-ethyl-1-methylnaphthalene. Cyclization of the acid through its chloride yielded 1-ethyl-7-acenaphthenone (V), which was reduced by means of aluminum isopropoxide to 1-ethyl-7-acenaphthenol. From the latter 3-ethyl-4,5-methylenephenanthrene was prepared by the same series of steps by which 4,5-methylenephenanthrene had been prepared from 7-acenaphthenol.[3]



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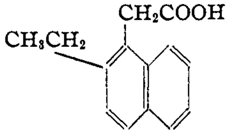

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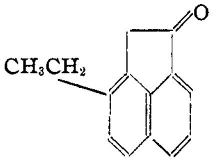

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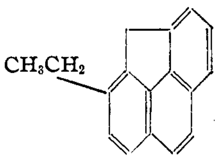

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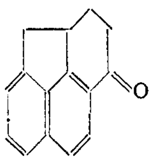
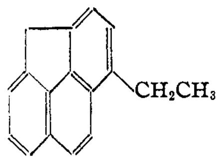


VII



VIII

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(1) Presented before the Organic Division at the meeting of the American Chemical Society, St. Louis, Missouri, April 11, 1941.

(2) From the Ph.D. dissertation of John Clark Sheehan.

(3) Bachmann and Sheehan, This Journal, **63**, 204 (1941).

(4) Fieser and Cason, *ibid.*, **62**, 1293 (1940).

We are grateful to the Abbott Laboratories for a fellowship to one of us (J. C. S.) which enabled us to carry on this investigation.

Experimental

Acetylation of 4,5-Methylenephenanthrene.—To a cooled solution (−5°) of 1.51 g. of anhydrous aluminum chloride in 20 cc. of nitrobenzene was added 0.56 cc. of acetic anhydride and 1 g. of finely powdered 4,5-methylenephenanthrene[3] with swirling of the solution. After twenty hours in a refrigerator, the mixture was hydrolyzed with ice and dilute hydrochloric acid and steam distilled. The product was dissolved in acetone, the solution was boiled with Norit and filtered, and the solvent was evaporated. Evaporative distillation of the residue at 220° and 0.5 mm. yielded 1 g. of a light straw-colored liquid which crystallized when cooled and scratched. Two recrystallizations of the product from methanol yielded 0.37 g. (30%) of **1-acetyl-4,5-methylenephenanthrene** (I); m. p. 152–153.5°.

Anal. Calcd. for $C_{17}H_{12}O$: C, 87.2; H, 5.2. Found: C, 87.5; H, 5.1.

When the filtrate was concentrated and cooled, fine needles of **3-acetyl-4,5-methylenephenanthrene** (II) crystallized. After recrystallization from methanol the compound melted at 93.5–96.5°; yield, 0.25 g. (21%).

Anal. Calcd. for $C_{17}H_{12}O$: C, 87.2; H, 5.2. Found: C, 87.9; H, 5.3.

1-Ethyl-4,5-methylenephenanthrene (VIII). (a) From **1-Keto-4,5-methylenetetrahydrophenanthrene.**—A solution of 0.5 g. of the cyclic ketone in 10 cc. of benzene was added to a chilled solution of ethylmagnesium bromide prepared from 0.55 cc. of ethyl bromide in 20 cc. of ether. After two hours of refluxing, the mixture was hydrolyzed with a solution of ammonium chloride containing a few drops of hydrochloric acid. The crude carbinol, obtained by evaporation of the ethereal solution at room temperature, was heated with 50 mg. of palladium-charcoal catalyst[5] at 280–300° in a nitrogen atmosphere for one hour, and the product was evaporatively distilled directly from the catalyst at 200° and 0.01 mm. By recrystallization from alcohol the hydrocarbon was obtained as colorless plates; yield, 0.405 g. (77%); m. p. 57.5–58.5°.

Anal. Calcd. for $C_{16}H_{14}$: C, 93.5; H, 6.5. Found: C, 93.4; H, 6.3.

The **picrate** crystallized from alcohol in orange needles; m. p. 113–113.5°.

Anal. Calcd. for $C_{23}H_{17}O_7N_3$: N, 9.2. Found: N, 9.3.

(b) From **1-Acetyl-4,5-methylenephenanthrene.**—A mixture of 50 mg. of this compound, 1 g. of amalgamated zinc (20-mesh), 3 cc. of hydrochloric acid, 0.5 cc. of acetic acid, 1 cc. of water and 2 cc. of toluene was refluxed for two days. The toluene layer was separated, the aqueous solution was diluted with water and extracted with benzene and the combined extracts were evaporated. Evaporative distillation of the residue followed by recrystallization from alcohol yielded 25 mg. (53%) of the hydrocarbon as colorless plates; m. p. 55–56°. The melting point when mixed with the hydrocarbon obtained in (a) was 55–57°, and the mixed melting point of the picrates was 112–113°.

1-Methyl-4,5-methylenephenanthrene.—This compound was prepared by the procedure employed in (a) above except that methylmagnesium iodide was used. From 0.5 g. of the cyclic ketone 0.45 g. of the hydrocarbon (m. p. 76–78°) was obtained. It crystallized from alcohol in colorless plates; m. p. 83.5–84.5°.

Anal. Calcd. for $C_{16}H_{12}$: C, 94.1; H, 5.9. Found: C, 94.1; H, 5.7.

The **picrate** crystallized from alcohol in orange needles; m. p. 161.5–162.5°.

Anal. Calcd. for $C_{22}H_{15}O_7N_3$: N, 9.7. Found: N, 9.6.

2-Ethyl-1-naphthaleneacetic Acid (IV).—Following the procedure employed by Cambron[6] on naphthalene, 28 g. of 2-ethylnaphthalene (obtained by Clemmensen reduction of 2-acetylnaphthalene) was condensed with 28 cc. of concentrated hydrochloric acid and 9 g. of paraformaldehyde in 24 cc. of acetic acid and 13.5 cc. of phosphoric acid. The yield of **1-chloromethyl-2-ethylnaphthalene** (III) (b. p. 145–158° at 5 mm.) was 26.8 g.

A mixture of the chloride, 270 cc. of acetone and a solution of 25 g. of potassium cyanide in 80 cc. of water was refluxed for twenty-four hours. After evaporation of the acetone, the nitrile was extracted with ether, the solution was washed with water, the solvent was removed and the nitrile boiled with a mixture of 200 cc. of acetic acid, 90 cc. of hydrochloric acid and 20 cc. of water for twelve hours. On cooling the solution deposited 12 g. of 2-ethyl-1-naphthaleneacetic acid as light tan needles. Retreatment of the residue, obtained by evaporation of the filtrate, with acetic and hydrochloric acid gave an additional quantity of the acid. The whole was then recrystallized from acetone–petroleum ether; yield, 16.45 g. (43% based on the 2-ethylnaphthalene); m. p. 155–158°. A sample after evaporative distillation at 180° and 0.01 mm. crystallized from acetone–petroleum ether in colorless needles; m. p. 161.5–163°.

Anal. Calcd. for $C_{14}H_{14}O_2$: C, 78.5; H, 6.5. Found: C, 78.1; H, 6.8.

Decarboxylation of the Acid.—The dried powdered sodium salt made from 0.5 g. of the acid was mixed intimately with 3 g. of powdered soda lime and the mixture heated with a free flame. The nearly colorless distillate of 2-ethyl-1-methylnaphthalene was converted to the picrate; after three recrystallizations from methanol, the picrate formed fine orange needles; m. p. 94–95° (reported,[7] 97°).

For comparison, 2-ethyl-1-methylnaphthalene was prepared in the following manner. To a solution of sodium methoxide prepared from 2.5 g. of sodium and 75 cc. of absolute methanol was added a solution of 2-carbomethoxy-1-tetralone[8] in 15 cc. of benzene. After a short period of refluxing, 13 cc. of ethyl iodide was added to the cooled mixture, and refluxing was continued for twelve hours; after two hours an additional 5 cc. of ethyl iodide was added. The ethylated product was isolated in the usual manner and the crude product was refluxed in a nitrogen atmosphere for six hours with a mixture of 40 cc. of acetic

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[5] Zelinsky and Turowa-Pollak, *Ber.*, **58**, 1295 (1925).

[6] Cambron, *Can. J. Research*, **17B**, 10 (1939).

[7] Brunner and Grof, *Monatsh.*, **64**, 76 (1934).

[8] Bachmann and Thomas, THIS JOURNAL, **63**, 598 (1941).

acid, 25 cc. of hydrochloric acid and 5 cc. of water. The mixture was poured into water, the oil which precipitated was extracted with ether, the solvent was removed and the residue was distilled; yield of colorless 2-ethyl-1-tetralone, 6.3 g. (78%); b. p. 140–150° at 10 mm. (reported,[7] 140–145° at 11 mm.).

The carbinol formed by treatment of 1.43 g. of 2-ethyl-1-tetralone with an excess of methylmagnesium iodide was heated with 0.2 g. of palladium–charcoal catalyst in a nitrogen atmosphere at 310° for one-half hour. The 2-ethyl-1-methylnaphthalene was evaporatively distilled at 0.2 mm. and its picrate recrystallized twice from methanol; yield, 1.37 g.; m. p. 94.5–95.5°. The mixed melting point with the picrate above was 94–95°.

1-Ethyl-7-acenaphthenone (V).—Ten cc. of thionyl chloride was added to a mixture of 10 g. of 2-ethyl-1-naphthaleneacetic acid, 30 cc. of dry ether and five drops of pyridine. After one-half hour at room temperature, the solvent and excess of reagent were removed under reduced pressure at 40°. The last trace of thionyl chloride was removed by a second evaporation after the addition of 15 cc. of benzene. The acid chloride was extracted with 250 cc. of dry benzene, and to the cooled solution was added 15 g. of powdered aluminum chloride. After one hour at room temperature, the mixture was treated with ice and hydrochloric acid. The benzene solution was washed with dilute hydrochloric acid, water, dilute ammonium hydroxide and again with water. After removal of the benzene the product was distilled at 1 mm.; from petroleum ether it crystallized in colorless prisms; yield, 7.78 g. (85%); m. p. 68–69°.

Anal. Calcd. for $C_{14}H_{12}O$: C, 86.7; H, 6.2. Found: C, 85.7; H, 6.2.

1-Ethyl-7-acenaphthenol.—A mixture of 5 g. of the ketone and 75 cc. of a *M* solution of aluminum isopropoxide in anhydrous isopropyl alcohol was refluxed for fifteen minutes, and then 50 cc. of liquid was distilled off slowly over a two-hour period. The residue was poured into 500 cc. of ice water containing 25 cc. of sulfuric acid, and the precipitated solid was filtered off, washed with water and with dilute ammonium hydroxide, and dissolved in hot benzene. The decolorized solution was concentrated and treated with petroleum ether; from the solution 4.32 g. (86%) of the product crystallized in colorless needles; m. p. 117–118°.

Anal. Calcd. for $C_{14}H_{14}O$: C, 84.8; H, 7.1. Found: C, 85.1; H, 7.2.

1-Ethyl-7-acenaphtheneacetic Acid.—Following the procedure described[3] the carbinol was converted through the bromide to the corresponding substituted acetic acid by means of the malonic ester synthesis. From 4 g. of the carbinol 3.18 g. (66%) of almost colorless acid was obtained; m. p. 112–113°. After two recrystallizations from benzene–petroleum ether a sample formed colorless prisms; m. p. 113–114°.

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 80.0; H, 6.7. Found: C, 80.4; H, 7.0.

6-Ethyl-1-keto-4,5-methylene-1,2,3,4-tetrahydrophenanthrene.—The Arndt–Eistert–Wolff reaction was carried out on 1.5 g. of the aforementioned acid in the manner described.[8] The resulting substituted propionic acid without purification was converted to its acid chloride and the latter was cyclized by means of stannic chloride according to the procedure described[3]; yield of cyclic ketone, 0.88 g. (60%); m. p. 105–107°. A sample after evaporative distillation at 180° and 0.01 mm. crystallized from acetone–petroleum ether in nearly colorless plates; m. p. 108–109.5°.

Anal. Calcd. for $C_{17}H_{16}O$: C, 86.4; H, 6.8. Found: C, 85.6; H, 6.7.

3-Ethyl-4,5-methylenephenanthrene (VI). (a) **From 6-Ethyl-1-keto-4,5-methylenetetrahydrophenanthrene.**—Following the procedure described[3] 0.5 g. of the ketone was reduced by the Clemmensen method to the tetrahydro compound, which was dehydrogenated by palladium on charcoal; yield of VI, 0.34 g. (74%); m. p. 81–82.5°. After evaporative distillation at 170° and 0.01 mm., the hydrocarbon crystallized from methanol in colorless diamond-shaped plates; m. p. 86.5–87.5°.

Anal. Calcd. for $C_{17}H_{14}$: C, 93.5; H, 6.5. Found: C, 93.1; H, 6.5.

The **picrate** crystallized from methanol in orange needles, m. p. 109–110.5°.

Anal. Calcd. for $C_{23}H_{18}O_6N_3$: N, 9.0. Found: N. 9.3.

(b) From **3-Acetyl-4,5-methylenephenanthrene.**—Clemmensen reduction of this compound was carried out by the procedure used on the 1-isomer; yield, 75%; m. p. 80–82°. From methanol the hydrocarbon crystallized in colorless plates; m. p. 84–85.5°. The melting point when mixed with the product obtained in (a) was 85–86°; a mixture of its picrate (m. p. 107.5–109°) with that above melted at 108–110°.

Summary

A general method for the preparation of alkyl derivatives of 4,5-methylenephenanthrene has been employed for the synthesis of 1- and 3-ethyl-4,5-methylenephenanthrene. 1-Methyl-4,5-methylenephenanthrene was also prepared.

4,5-Methylenephenanthrene is acetylated in nitrobenzene in the 1- and 3-positions.

Ann Arbor, Michigan Received July 19, 1941