

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

## Carcinogenic Hydrocarbons. 9,11-Dimethylbenz[*a*]anthracene and 8,9,11-Trimethylbenz[*a*]anthracene

BY BYRON RIEGEL AND JOHN G. BURR, JR.<sup>1</sup>

The possibility that some tumors may arise from abnormal steroid metabolism has stimulated a search for the carcinogenic agents. A plausible substance is 3,5-dimethylcholanthrene, the synthesis of which is described in the second paper of this series. The positions of interest in this hydrocarbon are C-5, where the steroid side chain would appear, and C-3, where the C-20 methyl group of the steroid side chain appears. To test this hypothesis further, the cumulative effect of methyl groups in the corresponding 9 and 11 positions<sup>2</sup> of the benz[*a*]anthracene system was investigated. The parent hydrocarbons selected are of varying carcinogenic activity so that any coupling effect by the addition of methyl groups in the 9 and 11 positions should be clearly evident. Two hydrocarbons that would best demonstrate this effect are 9,11-dimethylbenz[*a*]anthracene (I) and 8,9,11-trimethylbenz[*a*]anthracene (II).

These two hydrocarbons (I and II) have been prepared by a new method, which incorporates certain features of the Cook and Robinson synthesis of 11-methylbenz[*a*]anthracene<sup>3</sup> and of the Bachmann and Chmerda synthesis of 10-methylbenz[*a*]anthracene.<sup>4</sup> 3-Acetylphenanthrene (III) was condensed with diethyl succinate under the conditions of the modified Stobbe reaction, as developed by Johnson and his co-workers.<sup>5</sup> The yield of the half ester (IV) obtained in this reaction was found to depend upon the concentration of potassium *t*-butoxide in the solvent *t*-butyl alcohol, and to be nearly independent of the duration of heating or the excess of diethyl succinate. The use of a solution of potassium *t*-butoxide in *t*-butyl alcohol nearly saturated at the boiling point gave a 72% yield of the half ester (IV). The lactone (V) was produced in 70% yield by repeated hydrolysis of IV with a boiling mixture of acetic and hydrobromic acids. This lactone (V) was reduced to the corresponding  $\gamma$ -(3-phenanthryl)-valeric acid by several agents. Clemmensen reduction of the lactone produced the acid in 62–85% yields with a quantitative recovery of unreduced lactone. Catalytic reduction gave a 95% yield of the acid. The most convenient reducing agent, as determined by the results of the ensuing

cyclization, was a mixture of iodine and red phosphorus in glacial acetic acid. In all of these experiments, the substituted valeric acid was obtained as an oil, although it has been reported<sup>4</sup> as a solid melting at 75–77°. Cyclization of this non-crystalline acid, however, produced the known<sup>4</sup> 8-keto-11-methyl-8,9,10,11-tetrahydrobenz[*a*]anthracene (VI) in a 72–97% yield.

The ketone (VI) when condensed with methyl oxalate by the usual procedure<sup>4</sup> gave a quantitative yield of the glyoxalate (VII), which was decarbonylated by heating with powdered soft glass to the  $\beta$ -ketoester (VIII). The sodium salt of the keto ester was refluxed with methyl iodide, and the resulting methyl keto ester was repeatedly hydrolyzed with a boiling mixture of acetic and hydrochloric acids. 8-Keto-9,11-dimethyl-8,9,10,11-tetrahydrobenz[*a*]anthracene (IX) was thus obtained in a 75% yield from the ketone (VI), as colorless needles melting at 169–170°.

Reduction of this ketone (IX) with aluminum isopropoxide, and subsequent dehydration (through an intermediate 8-chloro compound) of the carbinol, led to 9,11-dimethyl-10,11-dihydrobenz[*a*]anthracene (X) which was obtained as colorless massive plates melting at 70–71°. The aromatization of X was accomplished by the Linstead solution method.<sup>6</sup> 9,11-Dimethylbenz[*a*]anthracene (I) forms colorless plates which melt at 154–154.5°.

The ketone (IX) was refluxed with an excess of methylmagnesium iodide, and the resulting carbinol (XI) was then heated with 5% palladium-charcoal at 300° to give the 8,9,11-trimethylbenz[*a*]anthracene (II) which was isolated (63% overall yield from IX) from the fusion mass as yellowish plates melting at 201–203.5°.

Samples of these hydrocarbons have been sent to Dr. M. J. Shear, of the National Cancer Institute, for biological testing.

### Experimental<sup>7</sup>

**Stobbe Half Ester (IV).**—A solution of 10.6 g. of potassium (cleaned and weighed under kerosene) in 150 ml. of anhydrous *t*-butyl alcohol was prepared by heating. This solution was mixed with 73.5 g. of diethyl succinate and 46.0 g. of 3-acetylphenanthrene<sup>8</sup> (m. p. 69–72°). The flask containing this mixture was repeatedly evacuated and filled with nitrogen, and the solution then refluxed for five hours in a nitrogen atmosphere. The warm solu-

(6) R. P. Linstead, A. F. Millidge, S. L. S. Thomas and A. L. Walpole, *J. Chem. Soc.*, 1146 (1937).

(7) All melting points were taken on a Fischer-Johns apparatus. Microanalyses by Patricia Craig and Nelda Mold, Northwestern University.

(8) Prepared by the method of E. Mosettig and J. van der Kamp, *THIS JOURNAL*, **52**, 3704 (1930), as modified by W. E. Bachman and C. H. Boatner, *ibid.*, **58**, 2097 (1936).

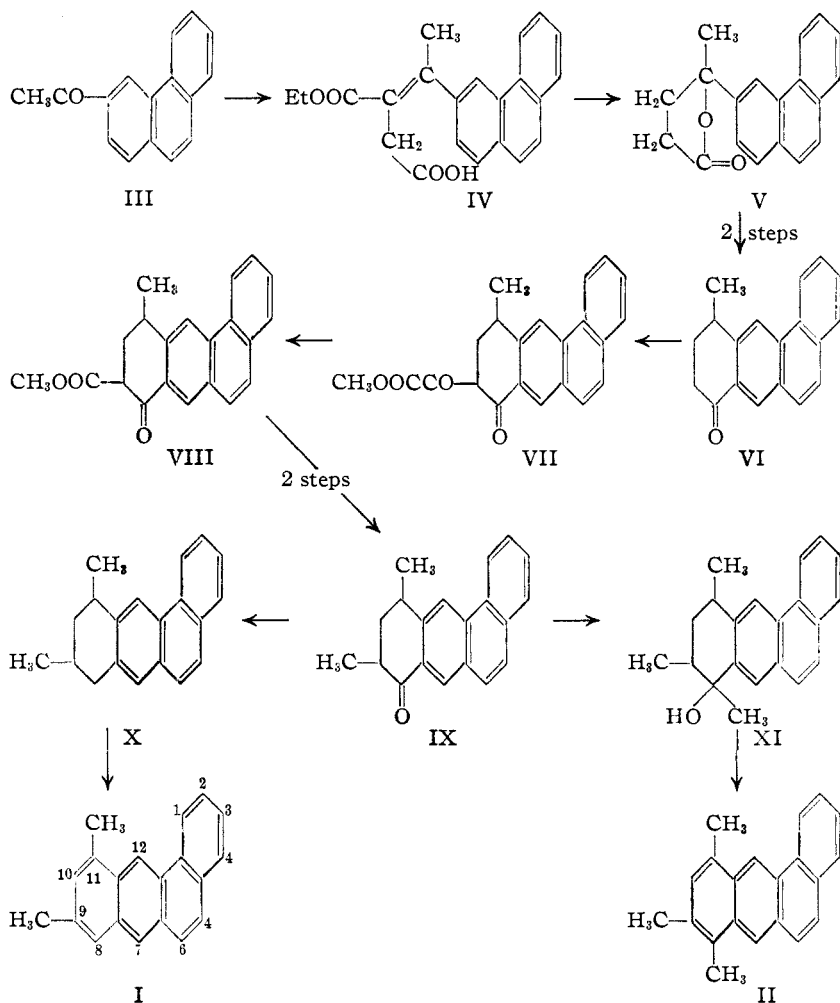
(1) Eastman Kodak Fellow, 1946–1947. Present address: Department of Chemistry, Miami University, Oxford, Ohio.

(2) The system of numbering used here is that recommended by "The Ring Index," Reinhold Publishing Corp., New York, N. Y., 1940, p. 381. Many of the previous investigators have named such compounds as derivatives of anthracene instead of benzanthracene.

(3) J. W. Cook and A. M. Robinson, *J. Chem. Soc.*, 505 (1938).

(4) W. E. Bachmann and J. M. Chmerda, *J. Org. Chem.*, **6**, 36 (1941).

(5) W. S. Johnson, A. Goldmann and W. P. Schneider, *THIS JOURNAL*, **67**, 1337 (1945).



tion was hydrolyzed with dilute hydrochloric acid, and organic solvents removed by distillation. The viscous product was dissolved in ether and the half ester extracted from the ether with dilute ammonium hydroxide. Acidification of the alkaline solution precipitated the half ester. From 85 g. of 3-acetylphenanthrene was obtained 98.5 g. (72%) of the half ester (IV) as a dark, clear, very viscous oil. The neutral material obtained by evaporation of the ether was crystallized from methanol and unreacted ketone (III) recovered as yellow needles, m. p. 64–67°.

Employment of a more dilute solution of potassium *t*-butoxide lowers the yield of half ester to 42–45% with proportionate recovery of the ketone (III).

**$\gamma$ -(3-Phenanthryl)-valerolactone (V).**—A suspension of 98.5 g. of the half ester (IV) in a mixture of 95 ml. of water, 188 ml. of 48% hydrobromic acid, and 285 ml. of glacial acetic acid was refluxed for six and one-half hours. The product of this reaction was a brown sandy solid which weighed 80.1 g. This solid was dissolved in chloroform, decolorized, and the solution concentrated and diluted with a large volume of ether. The lactone (V) crystallized (38.7 g.) as pale tan plates. The material remaining in solution was recovered and hydrolyzed with an acid mixture of the same composition and quantity as used originally. In this way, an additional 14.5 g. of the lactone was obtained, making a total yield of 53.2 g. (70%). Two crystallizations of this solid from chloroform-ether gave colorless needles melting at 150–151°.

*Anal.* Calcd. for  $C_{19}H_{16}O_2$ : C, 82.6; H, 5.80. Found: C, 82.2; H, 5.92.

**$\gamma$ -(3-Phenanthryl)-valeric Acid. A.**—To reduce the lactone (V), 18.64 g. of it with a mixture of 250 ml. of glacial acetic acid, 15 g. of red phosphorus, 5 g. of iodine, and 5 ml. of water was heated to boiling for six hours. This solution was filtered through sintered glass, and poured into two liters of water containing a little sodium bisulfite. The precipitated product was dissolved in ether-benzene, and the acid extracted from this solution with 10% potassium carbonate. The alkaline extract was acidified and the acid taken up in ether. Evaporation of the ether gave the acid as a clear brown viscous liquid weighing 18.86 g. (100%). When 38.7 g. of the lactone was reduced with the same quantities of reagents, 18.3 g. of the acid was obtained, and 20.0 g. of pure lactone was recovered. The reduction of 34 g. of the lactone with double the above quantities of reagents produced the acid in 84% yield, with recovery of 13% of lactone. The acid was identified by cyclization to the known 8-keto-9-methyl-8,9,10,11-tetrahydrobenz[a]anthracene (VI), as described below.

**B.** A 1.14-g. sample of the lactone was reduced by the use of 26 g. of amalgamated zinc, 20 ml. of water, 50 ml. of concentrated hydrochloric acid and 30 ml. of toluene. The reaction mixture was refluxed vigorously for forty-eight hours; during the first eight hours, 10-ml. portions of concentrated hydrochloric acid were added hourly. After cooling, the reaction mixture was

diluted with water and ether and worked up essentially as described in A. A yield of 0.98 g. (85%) of acidic material was obtained. Crystallization of the neutral fraction from chloroform-ether gave 0.21 g. (18%) of recovered lactone melting at 150–151°. On other runs the modified Clemmensen reduction did not give as consistent yields as the first method.

**C.** To a solution of 1.0 g. of the lactone in 50 ml. of glacial acetic acid containing 1.0 ml. of sulfuric acid was added 0.10 g. of palladium-charcoal catalyst. This solution was shaken with hydrogen at an initial pressure of 33.5 lb. At the end of four hours the catalyst was separated by filtration and most of the acetic acid removed under reduced pressure. The residue was poured into water and the precipitated oil extracted with ether and benzene. From the organic solution was obtained 0.95 g. (95%) of acidic material as a yellow viscous liquid. It was cyclized to the ketone in a nearly quantitative yield.

**8-Keto-11-methyl-8,9,10,11-tetrahydrobenz[a]anthracene (VI).**— $\gamma$ -(3-Phenanthryl)-valeric acid (18.86 g.) was dissolved in 100 ml. of benzene, and converted to the acid chloride with 19 g. of phosphorus pentachloride. The acid chloride was cyclized with 20 ml. of stannic chloride; after the bright orange crystalline complex had stood for one-half hour, it was hydrolyzed with a mixture of ice, hydrochloric acid, and ether. The product of this reaction was 16.0 g. (91.5%) of brown prisms. It was crystallized from ethanol-benzene to give 13.8 g. (79%) of shining tan crystals which melted at 126–130°. A sample of this ketone was dissolved in benzene, passed through alumina, and then crystallized from ethanol-benzene.

It then formed massive pale yellow prisms melting at 129–130.5° (lit.<sup>4</sup> 130–131.5°). The yield of crude ketone varied from 72–97%, depending upon the source of the acid.

The oxime crystallizes from alcohol as massive colorless plates melting at 192–193° (dec.).

*Anal.* Calcd. for  $C_{19}H_{17}ON$ : N, 5.09. Found: N, 4.88.

**8-Keto-11-methyl-8,9,10,11-tetrahydrobenz[a]anthracene-9-glyoxalate (VII).**—A mixture of 13.8 g. of the ketone (VI), the dry sodium methoxide from 2.21 g. of sodium, and 11.3 g. of dimethyl oxalate was dissolved in 500 ml. of dry benzene by shaking and gentle warming. After standing at room temperature for nine and one-half hours, the deep red solution was hydrolyzed with 100 ml. of water and the product extracted with 2% sodium hydroxide. The alkaline solution was acidified and the crude glyoxalate obtained as a clear deep red gum weighing 18.68 g. (100%). This gum crystallized on standing overnight. A portion was dissolved in acetone, decolorized with Nuchar and the first crop of crystals was again crystallized from ethanol. The glyoxalate forms pale chartreuse leaflets melting at 122–123.5° and gives a dark-brown color with alcoholic ferric chloride.

*Anal.* Calcd. for  $C_{22}H_{18}O_4$ : C, 76.3; H, 5.23. Found: C, 76.7; H, 5.57.

**8-Keto-11-methyl-9-carbomethoxy-8,9,10,11-tetrahydrobenz[a]anthracene (VIII).**—A mixture of 18.68 g. of the glyoxalate and 10 g. of powdered glass was heated at 180–190° for forty-five minutes at which time the evolution of gas had ceased. The keto-ester was extracted with benzene and crystallized from benzene-methanol to give 6.80 g. of brown prisms and 8.42 g. of an orange oil. Both fractions were suitable for the next step. A portion of the solid (in benzene solution) was passed through alumina, and crystallized from dioxane-methanol to give light tan prisms melting at 121–122.5°. It gives a green color with alcoholic ferric chloride.

*Anal.* Calcd. for  $C_{21}H_{18}O_3$ : C, 79.2; H, 5.71. Found: C, 79.7; H, 5.85.

**8-Keto-9,11-dimethyl-8,9,10,11-tetrahydrobenz[a]anthracene (IX).**—To a solution of sodium methoxide, prepared from 0.4 g. of sodium and a mixture of 5 ml. of methanol and 25 ml. of benzene, was added 2.50 g. of the crystalline keto ester (VIII). A pasty green solid precipitated. The solution was refluxed with 5 ml. of methyl iodide (a second 5-ml. portion was added after two hours) overnight. Volatile substances were stripped out by distillation, and the residue was taken up in benzene and passed through alumina. In some runs, the pink precipitate of sodium iodide formed in the reaction clogged the alumina column, so the suspension was filtered first. The methyl keto ester was obtained from the eluate as 2.72 g. (100%) of a yellow viscous oil. When cruder keto ester was methylated, the yield dropped to 84–89%.

The methyl keto ester (33.4 g.) was decarbomethoxylated by refluxing it for five hours with a mixture of 300 ml. of glacial acetic acid and 300 ml. of concentrated hydrochloric acid. The solvents were slowly distilled under reduced pressure, and the red granular residue (28.7 g.) was crystallized from benzene-methanol. The ketone, IX (19.5 g.), was obtained as pinkish needles. The material remaining in solution was recovered and refluxed with 200 ml. of the acid mixture. An additional 4.2 g. of the ketone was so produced. The total yield was 23.7 g. (75%); m. p. 169–172°. One crystallization from benzene-methanol, after treatment with Nuchar, gave a product which separated as colorless needles and melted at 169–170°.

*Anal.* Calcd. for  $C_{20}H_{18}O$ : C, 87.6; H, 6.61. Found: C, 87.5; H, 6.77.

The oxime crystallized in long silky needles from ethanol and melted at 220–220.5°.

*Anal.* Calcd. for  $C_{20}H_{18}ON$ : N, 4.84. Found: N, 4.89.

**8-Hydroxy-9,11-dimethyl-8,9,10,11-tetrahydrobenz[a]anthracene.**—Aluminum isopropoxide was prepared from 1.4 g. of aluminum wire and 190 ml. of dry isopropyl alcohol. Three grams of the ketone (IX) was dissolved in this solution, and isopropyl alcohol distilled out slowly. After 115 ml. of the alcohol had distilled during seven hours, a negative test for acetone was obtained in the distillate. Hydrolysis of the residual solution gave 3.19 g. of the carbinol as an oily solid.

**9,11-Dimethyl-10,11-dihydrobenz[a]anthracene (X).**—A rapid stream of dry hydrogen chloride was passed into a chilled solution of 3.19 g. of the above carbinol in 50 ml. of benzene containing 2.3 g. of calcium chloride. After twenty minutes the hydrogen chloride flow was stopped and the reaction mixture filtered through a sintered glass funnel. The solvent was evaporated and the residue heated *in vacuo* on a steam-bath. It evolved hydrogen chloride vigorously. The residue was sublimed at 1 mm., and the white solid sublimate crystallized from ethanol containing a few drops of water. The dihydrodimethyl hydrocarbon (X) was obtained as colorless, massive plates (1.44 g.) m. p. 68–70°. One crystallization from absolute ethanol raised the melting point to 70–71°.

*Anal.* Calcd. for  $C_{20}H_{18}$ : C, 93.0; H, 7.02. Found: C, 92.8; H, 6.76.

**9,11-Dimethylbenz[a]anthracene (I).**—To a solution of 1.06 g. of the dihydrodimethyl hydrocarbon (X) in 35 ml. of mesitylene was added 0.19 g. of 5% palladium-charcoal, and the resulting mixture was heated to vigorous boiling in a stream of carbon dioxide. The evolved gases were collected in a nitrometer. During three hours and twenty minutes, 110 ml. of hydrogen was collected. The product obtained from this reaction was crystallized from ethanol-benzene to give 0.75 g. of colorless plates melting at 154–155°. One crystallization from ethanol gave a product melting at 154–154.5°.

*Anal.* Calcd. for  $C_{20}H_{16}$ : C, 93.7; H, 6.29. Found: C, 93.7; H, 6.39.

The picrate crystallized from alcohol as deep red-brown needles which melted at 191–192°.

*Anal.* Calcd. for  $C_{20}H_{16} \cdot C_6H_3O_7N_3$ : N, 8.7. Found: N, 8.5.

The trinitrobenzene complex crystallized from alcohol as long thin orange needles which melted at 188–190°.

*Anal.* Calcd. for  $C_{20}H_{16} \cdot C_6H_3O_6N_3$ : N, 9.0. Found: N, 8.7.

**8,9,11-Trimethylbenz[a]anthracene (II).**—To a solution of methylmagnesium iodide prepared from 3.4 g. of methyl iodide and 0.67 g. of magnesium in 40 ml. of ether was added a solution of 1.64 g. of the ketone (IX) in 50 ml. of benzene. The reaction mixture was refluxed for one and one-half hours. The carbinol obtained after hydrolysis was a clear, amber, viscous liquid (2.29 g.). It was mixed with 200 mg. of 5% palladium-charcoal, protected with a nitrogen atmosphere, and during a one-hour period the temperature was gradually raised to 310°. The product was extracted from this melt and crystallized from benzene. There was obtained 1.02 g. (63%) of yellowish plates; m. p. 196–201°. A portion of this substance was crystallized twice more from ethanol-benzene, passed (in benzene solution) through an alumina column, and finally crystallized again from ethanol-benzene. 8,9,11-Trimethylbenz[a]anthracene thus purified has a melting point of 201–203.5°, and forms large regular faintly yellow diamond-shaped plates.

*Anal.* Calcd. for  $C_{21}H_{18}$ : C, 93.3; H, 6.71. Found: C, 93.5; H, 6.67.

The picrate crystallized as fine red-brown needles which melted at 190–191°.

*Anal.* Calcd. for  $C_{21}H_{18} \cdot C_6H_3O_7N_3$ : N, 8.4. Found: N, 8.3.

The trinitrobenzene derivative crystallized as orange micro-needles which melted at 199–200°.

*Anal.* Calcd. for  $C_{21}H_{18} \cdot C_6H_3O_6N_3$ : N, 8.7. Found: N, 8.5.

## Summary

1. 9,11-Dimethylbenz[*a*]anthracene and 8,9,11-trimethylbenz[*a*]anthracene have been pre-

pared by an improved synthesis for benz[*a*]anthracene derivatives.

EVANSTON, ILLINOIS

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Carcinogenic Hydrocarbons. 3,5-Dimethylcholanthrene<sup>1</sup>

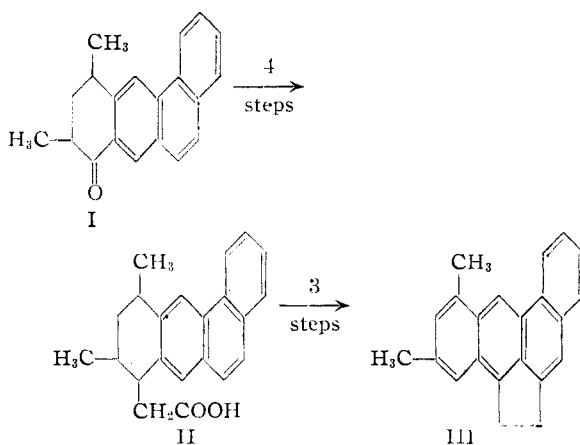
BY BYRON RIEGEL, JOHN G. BURR, JR.,<sup>2</sup> MICHAEL A. KUBICO AND MARVIN H. GOLD<sup>3</sup>

Since the preparation of methylcholanthrene from desoxycholic acid,<sup>4</sup> and from cholic acid<sup>5</sup> by a series of reactions whose types are known to occur in the animal body, it has been a natural speculation<sup>6</sup> that some tumors may be caused by carcinogenic agents produced by an abnormal metabolism of sterols or bile acids. The formation of substituted cholanthrenes from steroids requires a ring closure between the steroid side chain and ring C of the nucleus. The residue of the side chain will then occupy the 5 position in cholanthrene, and the C-20 methyl group of the steroid will be at the 3 position of cholanthrene (present system of numbering<sup>7</sup>). To date, 3,5-dialkylcholanthrenes have not been prepared and tested for carcinogenic activity. The biological reasons for desiring such information are obvious.

The first member of this series, 3,5-dimethylcholanthrene (III), has been prepared by general methods already recorded in the literature<sup>8</sup> for the preparation of substituted cholanthrenes. The starting material was 8-keto-9,11-dimethyl-8,9,10,11-tetrahydrobenz[*a*]anthracene (I).<sup>9</sup> By means of a Reformatsky reaction followed by dehydration, hydrogenation, and saponification, the ketone (I) was transformed into 9,11-dimethyl-8,9,10,11-tetrahydrobenz[*a*]anthryl-8-acetic acid (II). Cyclization of this acid by the action of stannic chloride upon the acid chloride produced a viscous liquid ketone which after reduction and dehydrogenation gave 3,5-dimethylcholanthrene. The action of liquid hydrogen fluoride upon the acid gave two products, one of which was an acetone-soluble viscous liquid, and the other (35%) was an acetone-insoluble substance crystallizing in bright yellow needles with a melting point of 267–270°. The physical properties and analysis of

this substance conform well with those expected for 1-keto-3,5-dimethylcholanthrene. It is evident that extensive dehydrogenation has occurred, presumably by hydrogen transfer during the cyclization, although the low hydrogen content found in the acid indicates the possibility that dehydrogenation occurred in an earlier step. At the time this experimental work was performed, the extent of the dehydrogenation was not suspected, and both the non-crystalline and the crystalline cyclization products were combined, after reduction of the keto group, and carried through to 3,5-dimethylcholanthrene which was obtained in fair yield from the mixture.

The reduction of the ketonic material was accomplished by the Martin modification of the Clemmensen reduction.<sup>10</sup> The reduction products from both the solid and the oily ketone were combined. Two methods were used for aromatization of this material: (1) the Linstead liquid phase method<sup>11</sup> which gave pure 3,5-dimethylcholanthrene (III) but in poor yield, and (2) the heating of the crude tetrahydro hydrocarbon with palladium-charcoal at 300°. This last method was distinctly superior, giving the 3,5-dimethylcholanthrene (III) in a 51% yield.



From ethanol or ethanol-acetone 3,5-dimethylcholanthrene crystallized as orange-yellow needles melting at 183–184°, but from acetone alone, it crystallized either as diamond-shaped plates or

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(8) (a) J. W. Cook and G. A. D. Haslewood, *J. Chem. Soc.*, 767 (1935); (b) E. Bergman and O. Blum-Bergmann, *THIS JOURNAL*, **59**, 1573 (1937); (c) W. E. Bachmann, *J. Org. Chem.*, **3**, 434 (1938);

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(9) B. Riegel and J. G. Burr, Jr., *THIS JOURNAL*, **70**, 1070 (1948).

(10) E. L. Martin, *ibid.*, **58**, 1438 (1936).

(11) R. P. Linstead, A. F. Millidge, S. L. S. Thomas and A. L. Walpole, *J. Chem. Soc.*, 1146 (1937).