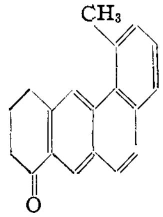
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF MICHIGAN]

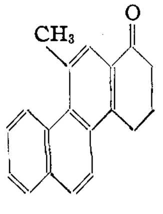
# The Synthesis of 5-Methyl-6,7-dimethylenechrysene and 1-Methylcholanthrene

BY W. E. BACHMANN AND S. R. SAFIR

It has been shown that 4-methylphenanthrene reacts with succinic anhydride to form a separable mixture of the 1- and 6-keto acids.[1] By the usual method of reduction and cyclization two ketones, I and II, were obtained. From the former we recently prepared 7-methylcholanthrene.[2] By the application of the same general procedure to the latter ketone, we have now accomplished the synthesis of 5-methyl-6,7-dimethylenechrysene (VI), a structural isomer of the methylcholanthrenes.

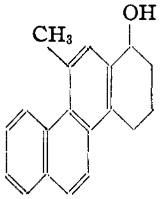


I

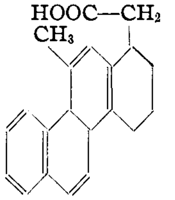


II

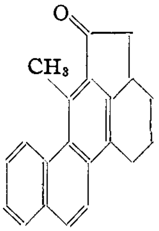
The ketone II was reduced by aluminum isopropoxide to the corresponding secondary alcohol (III), which was converted into the chloride by means of hydrogen chloride. A malonic ester synthesis on the chloride gave the substituted acetic acid IV which was cyclized through its acid chloride to the ketone V. Clemmensen reduction of the latter gave the tetrahydro derivative which was dehydrogenated with palladium–charcoal to 5-methyl-6,7-dimethylenechrysene (VI).



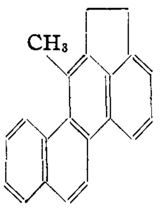
III



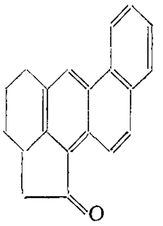
IV



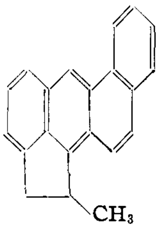
V



VI



VII



VIII

The new hydrocarbon is especially interesting because it is a 1,2,3,4-tetrasubstituted phenanthrene. When substituents are introduced into the 9- and 10-positions (which correspond to the 1- and 4-positions of the phenanthrene nucleus) of 1,2-benzanthracene, or into the 1- and 2-positions of 3,4-benzphenanthrene, powerful carcinogens are formed (*e. g.*, 9,10-dimethyl-1,2-benzanthracene[3] and 1,2,3,4-dibenzphenanthrene[4]). Moreover, Hewett has recently synthesized 5,6-dimethylchrysene,[5] which has proved to be an active carcinogen.

In order to obtain 1-methylcholanthrene (VIII), which has not hitherto been prepared, the requisite ketone (VII) was condensed with methylmagnesium iodide and the resulting carbinol was dehydrated and dehydrogenated with palladium–charcoal catalyst. In this process the first step is probably dehydration to give a compound with a double bond in the five-membered ring which accepts one mole of hydrogen given up by the tetrahydro ring during the treatment with palladium.[6] We believe the compound to have the structure assigned to it, although rearrangement with migration of the methyl group is not entirely excluded.

We are grateful to the Anna Fuller Fund for a generous grant which made this investigation possible.

## Experimental

**1-Hydroxy-11-methyl-1,2,3,4-tetrahydrochrysene** (III).—A mixture of 2.0 g. of 1-keto-11-methyl-1,2,3,4-tetrahydrochrysene,[1] 13 cc. of a *M* solution of vacuum-distilled aluminum isopropoxide in anhydrous isopropyl alcohol and 15 cc. of isopropyl alcohol was refluxed on a steam-bath for one-half hour and distilled through an upright condenser at such a rate that 13 cc. of distillate was collected in thirty

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[1] Bachmann and Edgerton, THIS JOURNAL, **62**, 2550 (1940).

[2] Bachmann and Safir, *ibid.*, **63**, 855 (1941).

[3] Bachmann and Chemerda, *ibid.*, **60**, 1023 (1938).

[4] Hewett, *J. Chem. Soc.*, 193 (1938).

[5] Hewett, *ibid.*, 293 (1940).

[6] For an analogous case see Bachmann and Carmack, THIS JOURNAL, **63**, 1685 (1941).

minutes. An additional 10 cc. of isopropyl alcohol was added, the solution was refluxed for ten minutes, and distilled at the rate of 1 cc. per minute for ten minutes, when a test for acetone was negative.[7]

The residue was poured into cold 5% sulfuric acid. The colorless carbinol was filtered, washed with water, then ammonia and finally water. A solution of the compound in acetone was filtered from a small quantity of insoluble material, diluted with water and concentrated. The carbinol separated as colorless rosets of needles melting at 149–150.5°; yield 1.66 g. (82%). The melting point was unchanged after a recrystallization from acetone–alcohol. The alcohol gives a purplish-black color with sulfuric acid.

*Anal.* Calcd. for $C_{19}H_{18}O$: C, 87.0; H, 6.9. Found: C, 87.0; H, 6.9.

**11-Methyl-1,2,3,4-tetrahydrochrysene-1-acetic Acid (IV).**—Dry hydrogen chloride was passed into a cold (5°) solution of 1.30 g. of the aforementioned carbinol in 75 cc. of benzene containing a small amount of calcium chloride. After forty-five minutes the excess hydrogen chloride and solvent were evaporated at 25° under reduced pressure. The colorless chloride (m. p. 132–133° with dec.) was used at once in the next step without purification.

To an ice-cold solution of sodio-malonic ester prepared from 0.57 g. of sodium, 35 cc. of absolute alcohol and 7.5 cc. of diethyl malonate was added a cold solution of the chloride in 75 cc. of benzene. The mixture was kept in a refrigerator for one day, at room temperature for one day, at 60° for three hours and finally was refluxed for five hours. The solvents were blown off with a jet of air, 25 cc. of 45% potassium hydroxide solution was added and the mixture was heated for one-half hour on a steam-bath. The solution obtained after dilution with 125 cc. of water was refluxed for three hours, cooled, filtered and poured into an excess of hydrochloric acid. The colorless malonic acid weighed 1.38 g. (77% based on the carbinol) and melted at 177–178° with decomposition.

The malonic acid was decarboxylated by heating it in a metal bath at 200–210° for fifteen minutes and the product was evaporatively distilled at 190° (0.01 mm.). The colorless 11-methyl-1,2,3,4-tetrahydrochrysene-1-acetic acid was recrystallized from benzene; yield 0.93 g. (78%); m. p. 188–190°. A sample after a second recrystallization from benzene melted at 190–191°.

*Anal.* Calcd. for $C_{21}H_{20}O_2$: C, 82.9; H. 6.6. Found: C, 82.8; H, 6.7.

**5-Methyl-1′-keto-6,7-dimethylene-7,8,9,10-tetrahydrochrysene (V).**—A mixture of 0.30 g. of the substituted acetic acid, 0.205 g. of phosphorus pentachloride and 5 cc. of benzene was heated on a steam-bath for twenty minutes when a clear, pale yellow solution was obtained. The phosphorus oxychloride and the solvent were removed by distillation under reduced pressure, and the acid chloride was dissolved in 6 cc. of carbon disulfide. The chloride was treated with 0.53 g. of anhydrous aluminum chloride, and the mixture was refluxed gently for forty-five minutes with occasional shaking. The dark green complex was hydrolyzed with ice and dilute hydrochloric acid and the carbon disulfide was distilled off. Benzene was added and the solution was washed with water, then with 5% potassium hydroxide solution and finally with water. The solvent was evaporated, the product was evaporatively distilled twice at 180° (0.01 mm.) and was recrystallized from chloroform–alcohol. The ketone was thus obtained in the form of colorless plates melting at 163–164° (vac.) and remelting at 164–164.5°; yield 0.23 g. (82%). The ketone gives an orange color with sulfuric acid.

*Anal.* Calcd. for $C_{21}H_{18}O$: C, 88.1; H, 6.3. Found: C, 87.9; H, 6.5.

**5-Methyl-6,7-dimethylenechrysene (VI).**—A mixture of 0.23 g. of the ketone V, 5 g. of amalgamated zinc (20 mesh), 5 cc. of concentrated hydrochloric acid, 5 cc. of toluene and 5 cc. of acetic acid was refluxed for thirty-six hours. Two portions of 9 cc. each of hydrochloric acid were added over this period. After separation of the organic layer, the aqueous layer was diluted with about three volumes of water and extracted once with benzene. Evaporation of the combined extracts yielded **5-methyl-6,7-dimethylene-7,8,9,10-tetrahydrochrysene** in nearly colorless crystals; m. p. 105–113°.

Without purification a mixture of the tetrahydro derivative and 0.025 g. of palladium–charcoal catalyst[8] was heated in a nitrogen atmosphere at 310° for forty-five minutes. The material which had sublimed up along the sides of the tube was washed down with benzene, the solvent was evaporated and the mixture was heated for an additional forty-five minutes. The product was separated from the catalyst by means of hot benzene, the solvent was removed and the product was evaporatively distilled at 160° (0.01 mm.). A benzene solution of the hydrocarbon was passed through a tower of alumina, the solvent was evaporated at 25° under reduced pressure, and the pale yellow product was recrystallized from acetone; yield 0.115 g.; m. p. 163–165° (vac.) (remelts at 167–168°). After a second evaporative distillation followed by a recrystallization from acetone, 0.075 g. of 5-methyl-6,7-dimethylenechrysene was obtained in the form of pale yellow needles melting at 167.5–168.3° (vac.) and remelting at 169–169.5°. Further crops of slightly less pure product (m. p. 166–167°) brought the total yield to 44% based on the ketone.

*Anal.* Calcd. for $C_{21}H_{16}$: C, 94.0; H, 6.0. Found: C, 93.7; H, 6.3.

**1-Methylcholanthrene (VIII).**—A cold solution of 0.54 g. of 1-keto-2a,3,4,5-tetrahydrocholanthrene (VII)[9] in 40 cc. of dry benzene was added to a cold solution of methylmagnesium iodide prepared from 0.24 g. of magnesium, 20 cc. of ether and 0.62 cc. of methyl iodide. The clear yellow solution which was formed was kept in a refrigerator for twelve hours and was then hydrolyzed with cold ammonium chloride solution and dilute hydrochloric acid. The organic layer was separated, washed well with water and the solvents were evaporated at 25° under diminished pressure. In this manner **1-methyl-1-hydroxy-2a,3,4,5-tetrahydrocholanthrene** was obtained in the form of nearly colorless threads (m. p. 60–70°).

Without purification a mixture of the crude alcohol and 0.050 g. of palladium–charcoal catalyst was heated in a nitrogen atmosphere at 300–320° for one hour. The sublimed material was returned to the bottom of the tube in

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[7] Lund, *Ber.*, **70**, 1520 (1937).

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

[9] Bachmann, *J. Org. Chem.*, **3**, 434 (1938).

the usual manner and the mixture was heated for an additional forty minutes. After separation of the product from the catalyst by means of hot benzene, the latter was removed and the residue was evaporatively distilled at 175° (0.01 mm.). The orange-yellow hydrocarbon (0.450 g.; m. p. 166–168°) was converted into its picrate in benzene–petroleum ether and the picrate was recrystallized once from benzene–petroleum ether; m. p. 148.5–150° (vac.).

*Anal.* Calcd. for $C_{21}H_{16}\cdot C_6H_3O_7N_3$: N, 8.5. Found: N, 8.4.

A benzene solution of the regenerated hydrocarbon was passed through a tower of alumina, the solvent was evaporated in the usual manner and the residue was recrystallized from acetone–alcohol from which the hydrocarbon separated in the form of orange-yellow cubes; yield 0.355 g. (67% based on the ketone (VII)); m. p. 169–170°. A mixed melting point of 1-methylcholanthrene and cholanthrene (169–170°) was 144–155°.

*Anal.* Calcd. for $C_{21}H_{16}$: C, 94.0; H, 6.0. Found: C, 93.8; H, 6.1.

## Summary

The synthesis of 5-methyl-6,7-dimethylenechrysene, a structural isomer of the methylcholanthrenes, is described. The preparation of 1-methylcholanthrene is also reported.

The new hydrocarbons will be tested for carcinogenic activity.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME]

# The Preparation of Some *p*-Dialkylbenzenes[1]

BY CHARLES E. WELSH AND G. F. HENNION

## Introduction

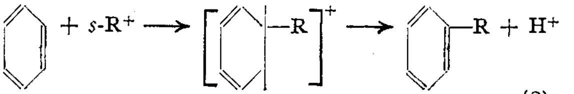
The alkylation of monoalkylbenzenes by the alcohol–boron fluoride–phosphorus pentoxide method, previously described,[2] has now been found to be an excellent method for the preparation of certain *p*-dialkylbenzenes. Toluene and ethylbenzene have been so alkylated and give excellent yields with normal alcohols, particularly in the range $C_4$ to $C_{12}$. The advantage of the use of co-condensing agents with boron fluoride in certain cases has again been noted. *n*-Butyl alcohol does not alkylate toluene under the influence of boron fluoride alone, but when phosphorus pentoxide is used also, a 90% yield of *p*-*s*-butyltoluene is obtained. It has been found better to omit the phosphorus pentoxide, however, when the same alkylation is performed with *s*-butyl alcohol. In general the normal primary alcohols give the best yields, apparently because they react more slowly and do not give the olefin polymer and high boiling residues so often obtained with the easily dehydrated alcohols.

The direct dialkylation of benzene was studied with *n*-butyl and *n*-amyl alcohols. These gave 68% and 40% yields, respectively, of the *p*-di-*s* products, somewhat less satisfactory than the two step processes.

With one exception all of the alkylations resulted in selective para substitution, as shown by the fact that products distilled over narrow temperature ranges, with substantially constant refractive indices, and oxidized to terephthalic acid. Samples of the latter gave only faint fluorescein tests and yielded dimethyl terephthalate of correct melting point. The ethylation of toluene gave material boiling over a two degree range with continuous drift in the refractive index, approximately from the para to the ortho values. The diacid obtained on oxidation gave a pronounced fluorescein test.

The reaction products are those which would be obtained by dehydration of the alcohol to olefin with para addition of the latter. Thus the normal primary alcohols introduce the corresponding secondary alkyl group. Actually the olefin mechanism[3] is no longer tenable as shown by the work of Whitmore[4] and Price[5] as well as recent experiments in this Laboratory,[1] all of which favor the positive fragment theory.

$$n\text{-ROH} + BF_3 \longrightarrow s\text{-R}^+ + (HO \longrightarrow BF_3)^- \quad (1)$$



(2)

The experimental conditions and products are described in Tables I, II and III.

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(1) Paper XXV on organic reactions with boron fluoride: previous paper, THIS JOURNAL, **63**, 1722 (1941).

(2) Toussaint and Hennion, *ibid.*, **62**, 1145 (1940).

(3) Sowa, *et al.*, *ibid.*, **57**, 709 (1935); **59**, 470, 1204 (1937); **60**, 125, 654 (1938).

(4) Whitmore, *ibid.*, **54**, 3274 (1932).

(5) Price *et al.*, *ibid.*, **60**, 2499 (1938); **61**, 1595 (1939); **62**, 3105 (1940).