ground with 25 mg. of basic copper carbonate and heated under vacuum in a bath which was eventually brought to a temperature of 300°. The dark distillate (294 mg.) was extracted three times with cold absolute alcohol and the undissolved material taken up in benzene. After treatment with Norit and concentration, 65 mg. (8.1%) of light brown crystals separated. Purification by adsorption of impurities on alumina gave a yellow crystalline powder, m. p. 167.5–168.5°, which gave no depression when mixed with known cholanthrene, m. p. 166.5–168.5°. The picrate agreed in m. p. and appearance with the specimen described by Cook, Haslewood and Robinson.[7]

Summary

1-Acetoacenaphthene was converted to 1-acenaphthylacetic acid via 1-acenaphthoic acid by the Arndt–Eistert reaction and, more conveniently, by the Willgerodt process of heating the ketone with yellow ammonium sulfide. The acetic acid was condensed successfully with both *o*-chloro and *o*-nitrobenzaldehyde, but only the second of the products could be utilized for effecting a phenanthrene ring closure. Although the Pschorr reaction proceeded very poorly, the 7-carboxy derivative of cholanthrene was isolated through the ester in quantity sufficient for an investigation of its possible biological actions.

The hydrogen fluoride acylation of acenaphthene with phenylacetic acid and *o*-bromophenylacetic acid does not provide a practical route to intermediates suitable for the synthesis of cholanthrenes.

CONVERSE MEMORIAL LABORATORY
CAMBRIDGE, MASSACHUSETTS RECEIVED MARCH 21, 1940

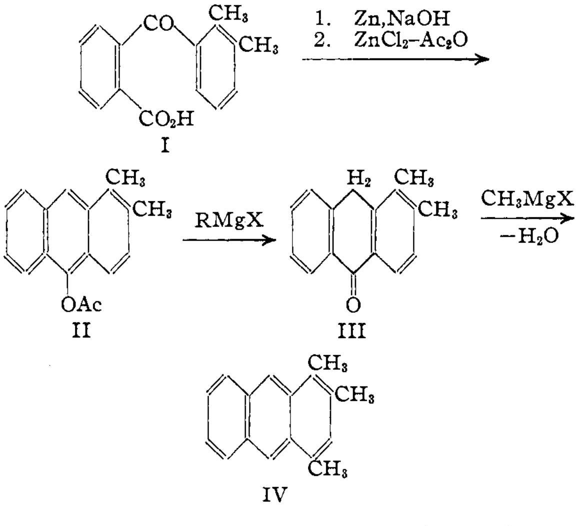
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

meso-Alkyl Anthracenes

BY LOUIS F. FIESER AND THOMAS G. WEBBER

In continuation of previous studies of model compounds structurally related to the more potently active carcinogens,[1] we sought to synthesize certain additional substituted 1,2-dialkyl anthracenes of types corresponding to known 1,2-benz derivatives of marked carcinogenic activity. The 1,2-dimethyl and 1,2-cyclopenteno derivatives of 5,10-aceanthrene were synthesized in earlier work[2] for comparison with cholanthrene, and the cyclopenteno compound was found by Shear (see ref. 1) to have definite if weak carcinogenic properties. It was hoped in the present work to obtain 1,2,10-trimethylanthracene and 1,2,9,10-tetramethylanthracene for comparison with 10-methyl-1,2-benzanthracene[3] and 9,10-dimethyl-1,2-benzanthracene,[4] respectively. The trimethyl compound was synthesized without difficulty, but the method tried for the preparation of the higher homolog proved unsatisfactory. Badger, Cook and Goulden[5] have recently reported an unsuccessful attempt to synthesize the same hydrocarbon by another method.

1,2,10-Trimethylanthracene was synthesized starting with the keto acid I[5] from *vic.*-bromo-*o*-xylene and phthalic acid. After reduction with zinc and alkali, cyclization with zinc chloride and acetic acid–anhydride[6] gave the anthranyl acetate (II), and on cleavage by the Grignard reagent the anthranol isomerized readily to the anthrone. A methyl group was then easily introduced at the 10-position. As with anthracene and a number of its derivatives,[7] the yellow trimethyl compound IV forms a colorless dimer when exposed to sunlight in solution.



A projected synthesis of the desired tetramethyl

---

[1] For summary and review, see Fieser, *Am. J. Cancer*, **34**, 37 (1938).

[2] Fieser and Hershberg, THIS JOURNAL, **59**, 394 (1937).

[3] Fieser and Newman, *ibid.*, **58**, 2376 (1936).

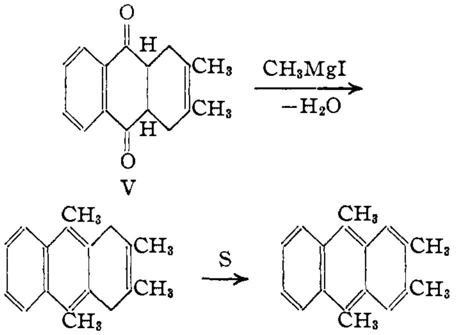
[4] Bachmann and Chemerda, *ibid.*, **60**, 1023 (1938).

[5] Badger, Cook and Goulden, *J. Chem. Soc.*, 16 (1940).

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

[7] Houben, "Das Anthracen und die Anthrachinone," Verlag Georg, Thieme, Leipzig, 1929, p. 133.

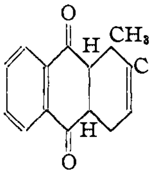
compound was tested first in a case requiring more readily available starting materials. 2,3-Dimethylbutadiene was added to α-naphthoquinone and the product (V)[8] treated with excess methylmagnesium iodide. The reaction proceeded well and a crystalline dihydroanthracene (VI) was obtained on dehydration of the crude diol. Dehydrogenation to VII was accomplished satisfactorily with the use of sulfur. The substance forms an amorphous dimer from which it can be regenerated in part by vacuum distillation.



V

VI VII

3-Methylpentadiene-2,4 was then prepared according to Fisher and Chittenden[9] and found to add smoothly to α-naphthoquinone. The addition product VIII, however, behaved quite differently from the isomer in the Grignard reaction and no diol or hydrocarbon could be isolated after treatment with methylmagnesium chloride or iodide. Starting with 1,2-dimethylanthraquinone, Badger, Cook and Goulden[5] obtained a diol but found its dimethyl ether resistant to cleavage with sodium.



VIII

Experimental Part[10]

o-(2,3-Dimethylbenzoyl)-benzoic acid (I) was prepared from the Grignard reagent from 13 g. of *vic.*-bromo-*o*-xylene,[2] condensed with 30 g. of phthalic anhydride in ether–benzene. After hydrolysis and steam distillation the keto acid was precipitated from a steamed and filtered alkaline solution by pouring this into ice and hydrochloric acid. Crystallization from benzene–hexane gave 7 g. (32%) of colorless prisms, m. p. 129–131°, and after three further crystallizations the substance melted at 132–133° and remelted at 139.5–140.5°.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.39; H, 5.71.

Badger, Cook and Goulden[5] used a smaller proportion of anhydride and obtained a much higher yield. They report the m. p. 126–127°.

o-(2,3-Dimethylbenzyl)-benzoic Acid.—The keto acid (3.5 g.) was refluxed in 50 cc. of 2 N sodium hydroxide with 3.5 g. of zinc dust for forty-seven hours, 45 cc. more alkali being added in three portions. The precipitated acid when crystallized from methanol afforded in two crops 3.1 g. (94%) of colorless prisms, m. p. 175–177°. Fully purified, the acid melted at 177.2–177.8°.

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.91. Found: C, 79.80; H, 6.89.

The **lactone of o-(2,3-dimethyl-α-hydroxybenzyl)-benzoic acid** was isolated from the reaction mixtures resulting after shorter periods of heating by extraction of the acid with soda solution. The residual material crystallized from dilute alcohol as colorless prisms, m. p. 127–128°.

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.47; H, 6.07.

1,2-Dimethylanthranyl-10-acetate (II).—A solution of 7.3 g. of the above acid in 45 cc. of acetic acid and 30 cc. of acetic anhydride containing 0.5 g. of anhydrous zinc chloride was refluxed for one hour and water was then added cautiously to the point of saturation. On cooling, 6.5 g. (81%) of light yellow prisms of the acetate separated, m. p. 152–154°. After four recrystallizations from dilute acetic acid the substance melted at 158.1–158.7° and had a greenish yellow tinge.

Anal. Calcd. for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.46; H, 6.12.

1,2-Dimethyl-10-anthrone (III).—The solid anthranyl acetate (6.5 g.) was added to the Grignard reagent from 3.6 g. of magnesium and excess n-butyl bromide and after displacement of the ether with benzene refluxing was continued for one hour. After hydrolysis, two crystallizations from benzene afforded 3 g. (55%) of the anthrone, m. p. 169–170°. The further purified material formed colorless prisms, m. p. 170.3–171.3°. The properties of the substance and its behavior in the Grignard reaction indicate the ketonic structure; the tautomeric anthranol was not encountered.

Anal. Calcd. for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.50; H, 6.48.

1,2,10-Trimethylanthracene.—A solution of 1.05 g. of the anthrone in 50 cc. of benzene was added to the reagent from 0.62 g. of magnesium and excess methyl bromide in ether and the mixture was refluxed for two hours before hydrolysis. The washed and dried organic layer was evaporated to dryness on the hot-plate to dehydrate the carbinol, and the residue was crystallized from hexane, giving 0.89 g. (77%) of the hydrocarbon as yellow needles, m. p. 88–90°. This was converted to the **picrate**, which crystallized from alcohol in minute dark brown needles, m. p. 138.5–139.5°. The regenerated hydrocarbon (alumina tower) was yellow and melted at 90.6–91.4°.

Anal. Calcd. for $C_{17}H_{16}$: C, 92.68; H, 7.32. Found: C, 92.60; H, 7.49.

---

[8] I. G. Farbenindustrie A.-G., British Patent 320,375 (1930).

[9] Fisher and Chittenden, *Ind. Eng. Chem.*, **22**, 869 (1930).

[10] All melting points are corrected.

The **trinitrobenzene derivative** formed scarlet needles, m. p. 169.6–170.2°, from alcohol.

On exposing an alcoholic solution of the hydrocarbon to the sunlight for three weeks prisms of the colorless **dimer** were deposited. Recrystallized from benzene-alcohol the substance melted at 222–226°.

Anal. Calcd. for $C_{34}H_{32}$: C, 92.68; H, 7.32. Found: C, 92.91; H, 7.28.

2,3-Dimethylbutadiene-α-Naphthoquinone (V).—A solution of 5 g. of α-naphthoquinone and 10 cc. of the diene in 20 cc. of alcohol was refluxed for three hours, and on cooling the addition product separated as fine, colorless needles. This material was collected, washed with alcohol, and dried in vacuum at 50°; m. p. 148.5–149.1°; yield, 7.25 g. (95%).

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.88; H, 6.79.

2,3,9,10 - Tetramethyl - 1,4 - dihydroanthracene (VI).—A solution of 7.2 g. of V in 50 cc. of warm benzene was added to a stirred solution of the methylmagnesium iodide from 4.2 g. of magnesium in about 70 cc. of ether-benzene and stirring was continued at room temperature for three hours. After hydrolysis and removal of the solvent the oily diol was heated to 140° to effect dehydration. On adding a little alcohol to the dark residual oil the hydrocarbon crystallized, and when collected and washed with a small volume of cold alcohol was obtained in a nearly colorless condition suitable for dehydrogenation; m. p. 165–170°, yield 3.0 g. (42%). A sample was purified by passage in benzene solution through a tower of alumina and crystallization from benzene-hexane. It formed colorless needles, m. p. 175.3–176.3°; the solutions showed intense blue fluorescence in ultraviolet light.

Anal. Calcd. for $C_{18}H_{20}$: C, 91.47; H, 8.53. Found: C, 91.42; H, 8.70.

The hydrocarbon appears to undergo ready disproportionation or other change, for further crystallized samples had higher and broader melting ranges. The **picrate** crystallized in small, dark brown needles from benzene-hexane, m. p. 149.2–149.9°. The **trinitrobenzene derivative** was obtained from benzene as scarlet needles, m. p. 150.8–151.8°.

Anal.[11] Calcd. for $C_{18}H_{20} \cdot C_6H_3O_6N_3$: N, 9.35. Found: N, 9.25.

2,3,9,10-Tetramethylanthracene.—The dihydride VI (3 g.) was heated with 0.4 g. of sulfur to 325° in one-half hour, when the evolution of gas had ceased. After heating with a pinch of zinc dust for fifteen minutes the dark residue was extracted with benzene and the solution was put through a tower of alumina. The hydrocarbon crystallized from alcohol-benzene in brownish-yellow plates, m. p. 137–139°; yield 1.65 g. (55%). On using palladium charcoal for dehydrogenation the yield dropped to 25%. The further purified hydrocarbon formed dark yellow plates, m. p. 139.4–140.2°, from benzene-hexane.

Anal. Calcd. for $C_{18}H_{18}$: C, 92.26; H, 7.74. Found: C, 92.14; H, 7.71.

Exposure of solutions of the hydrocarbon to light resulted in the separation of an amorphous, brown **dimer** which melted at about 270°. On heating this at 2 mm. pressure in a bath at 210° the monomeric form distilled and was recovered in 63% yield.

The **picrate** formed dark brown needles from benzene-hexane, m. p. 177.3–178.3°. The **trinitrobenzene derivative** separated from benzene in scarlet needles, m. p. 188.8–189.3°.

Anal.[11] Calcd. for $C_{18}H_{18}.C_6H_3O_6N_3$: N, 9.39. Found: N, 9.69.

3-Methylpentadiene-α-Naphthoquinone (VIII).—The diene (b. p. 77–80°) was prepared by the method of Fisher and Chittenden[9] in over-all yield of 2.3%. The keto alcohol resulting from the condensation of acetaldehyde with methyl ethyl ketone could not be reduced satisfactorily to the 1,3-glycol either with Adams catalyst at a low pressure or with Raney nickel in the high pressure apparatus. With a combination of the two catalysts reduction was effected at 86° and 1500 lb. (100 atm.) pressure in 75% yield, based on starting material consumed.

A solution of 10 g. of α-naphthoquinone and 6.9 g. of the diene in 20 cc. of alcohol was refluxed for three hours, and after cooling to 0° 12.3 g. (81%) of the addition product separated as fine, colorless needles, m. p. 100.2–101.4°. Recrystallization from benzene-alcohol raised the m. p. to 101–101.7°.

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.91; H, 6.86.

The condensation of this substance with methylmagnesium iodide or chloride was tried under various conditions but in no case could a product having the properties of a diol be isolated. In the case of the iodide a reaction occurred and two ill-defined products of lower carbon content than the starting material were encountered. One of these, amounting to nearly half the weight of starting material, formed colorless needles melting in the range 140–154° (found: C, 78.35, 78.35; H, 7.87, 7.84). With methylmagnesium chloride the only product isolated was **1,2-dimethylanthraquinone,** which was readily obtained from the addition product by air oxidation in alcohol solution to which a trace of alkali had been added. Purified by chromatographic adsorption and crystallized from benzene-hexane, the quinone melted at 157.8–158.2° (Barnett and Carlisle,[12] m. p. 156°).

Summary

1,2,10-Trimethylanthracene, desired for comparison with the carcinogenically active 10-methyl-1,2-benzanthracene, was synthesized by known methods from *vic.*-bromo-*o*-xylene and phthalic anhydride. 2,3,9,10-Tetramethylanthracene was obtained readily from the addition product of α-naphthoquinone and 2,3-dimethylbutadiene by reaction with methyl Grignard reagent, dehydration of the resulting diol, and dehydrogenation. An attempted synthesis of the 1,2,9,10-isomer by this route failed at the stage of interaction with the Grignard reagent.

CONVERSE MEMORIAL LABORATORY
CAMBRIDGE, MASSACHUSETTS
RECEIVED MARCH 22, 1940

---

[11] Microanalysis by Herbert S. Wight.

[12] Barnett and Carlisle, *Ber.*, **64**, 535 (1931).