[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF DUKE UNIVERSITY]

9-Methyl- and 10-Methyl-1,2-benzanthracene

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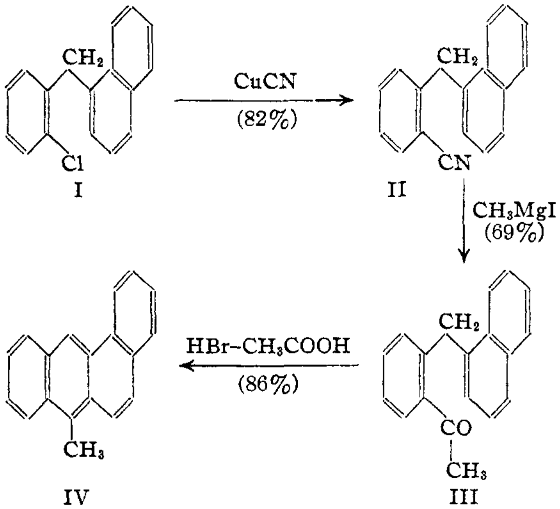
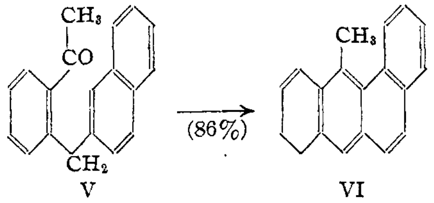
Recently[1] we have shown that *o*-benzylphenyl ketones may be cyclized to form 9-alkyl- and 9-arylanthracene hydrocarbons. The demonstrated[2] importance of *meso* substitution as a source of carcinogenic activity in derivatives of 1,2-benzanthracene made it of interest to attempt the application of the new reaction to this series.

Two carcinogenic hydrocarbons, 9-methyl- and 10-methyl-1,2-benzanthracene have now been prepared in this manner.



In the synthesis of the 10-methylbenzanthracene (IV), the crude carbinol produced by the action of α-naphthylmagnesium bromide on *o*-chlorobenzaldehyde was reduced with red phosphorus and iodine to give 1-(*o*-chlorobenzyl)-naphthalene (I). By action of cuprous cyanide, this was converted to a nitrile (II) which upon treatment with methylmagnesium iodide afforded *o*-(1-naphthylmethyl)-acetophenone (III). Cyclization to the hydrocarbon (IV) was effected in good yield by refluxing the ketone (III) for three days in a mixture of acetic and hydrobromic acids. The over-all yield of the pure hydrocarbon was 29%, calculated from the *o*-chlorobenzaldehyde taken.

The synthesis of 9-methyl-1,2-benzanthracene (VI) was accomplished similarly, starting from β-naphthylmagnesium bromide or iodide and *o*-chlorobenzaldehyde. Reduction of the carbinol, conversion to the nitrile and treatment with methylmagnesium iodide gave *o*-(2-naphthylmethyl)-acetophenone (V), which was cyclized easily to the expected hydrocarbon (VI).



Although the yield in the ring closure was exactly the same, the over-all yield was somewhat less than in the preparation of the isomer. It is interesting to note that only twenty-four hours were required for cyclization, undoubtedly due to the great reactivity of the *alpha* position in the naphthalene nucleus.[3] A parallel observation has been made in the case of the Elbs reaction.[4]

We feel that the new synthesis not only affords an eminently satisfactory route to 10-methyl-1,2-benzanthracene, but gives promise of providing a useful tool for the synthesis of new carcinogenic and antigenic compounds.

The author is indebted to Professor Louis F. Fieser, who has established the identity of the hydrocarbons prepared by comparing them with authentic specimens.

Experimental

1-(*o*-Chlorobenzyl)-naphthalene (I).—A Grignard reagent was prepared in dry ether from 45.5 g. of α-naphthyl bromide and 5.4 g. of magnesium. To this was added an ethereal solution containing 28.1 g. of *o*-chlorobenzaldehyde and the mixture allowed to stand overnight. The mixture was then decomposed with a 20% solution of ammonium chloride and the ethereal layer separated and concentrated on the steam-bath. The residue was dissolved in 500 cc. of acetic acid, and 10 g. of iodine, 10 g. of red phosphorus and 50 cc. of water added. This mixture was refluxed for twenty-seven hours and then the excess phosphorus was filtered off by suction. A quantity of ice was added to the filtrate and the mixture extracted with ether. The ethereal extract was freed of acetic acid and iodine by extraction with iced 10% sodium hy-

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(1) THIS JOURNAL, **62**, 486 (1940).

(2) *E. g.*, Fieser and Newman, *ibid.*, **58**, 2376 (1936); Fieser and Hershberg, *ibid.*, **59**, 1028 (1937); Newman, *ibid.*, **59**, 1003 (1937); Bachmann, Kennaway and Kennaway, *Yale J. Biol. Med.*, **11**, 97 (1938).

(3) The cyclization of *o*-benzylacetophenone (ref. 1) requires four days.

(4) Clar, *Ber.*, **62**, 350, 1387 (1929); Fieser and Dietz, *ibid.*, **62**, 1827 (1929).

droxide solution, dried, concentrated and the residue distilled under reduced pressure. The product was a water-white liquid, b. p. 189–192° (2 mm.); yield 30.5 g. (60%).

Anal.[5] Calcd. for $C_{17}H_{13}Cl$: C, 80.76; H, 5.19. Found: C, 80.88; H, 5.12.

***o*-(1-Naphthylmethyl)-benzonitrile** (II).—A mixture of 25.3 g. of the chloro compound (I) obtained above with 10.8 g. of cuprous cyanide and 10 cc. of pyridine was heated under an air condenser for thirty hours at 250–260°. It was then poured on a mixture of ice and sodium hydroxide and the mixture extracted with benzene. The benzene layer was filtered and then washed with dilute hydrochloric acid, water, and finally saturated sodium chloride solution. The benzene was then evaporated and the residue distilled under reduced pressure. The product was a viscous amber-colored oil, b. p. 216–217° (3 mm.), which solidified upon seeding. This material was pure enough for further reactions. A sample crystallized from ether–petroleum ether was obtained as stout prisms, m. p. 59–60°.

Anal. Calcd. for $C_{18}H_{13}N$: C, 88.85; H, 5.39. Found: C, 88.90; H, 5.46.

***o*-(1-Naphthylmethyl)-acetophenone** (III).—A Grignard reagent was prepared from 28.4 g. of methyl iodide and 4.9 g. of magnesium. Most of the ether was distilled off and 12.2 g. of the nitrile (II) obtained above added in 150 cc. of dry benzene and the mixture refluxed overnight. After decomposition of the reaction mixture with ammonium chloride solution, the imine was extracted from the benzene layer with 2 *N* hydrochloric acid. To this acid extract, 50 cc. of concentrated hydrochloric acid was added and the mixture refluxed for one hour. The ketone thus liberated was taken up in ether. The ethereal extract was washed, dried and concentrated. The residue, distilled under reduced pressure, gave 8.9 g. (69%) of a viscous, nearly colorless liquid, b. p. 216–217° (3 mm.). This liquid was used for the cyclization experiments, but the ketone could be crystallized from ether–petroleum ether as colorless blades, m. p. 39–40°.

Anal. Calcd. for $C_{19}H_{16}O$: C, 87.66; H, 6.19. Found: C, 87.53; H, 6.29.

10-Methyl-1,2-benzanthracene (IV).—Two grams of the ketone (III) was refluxed for three days in a mixture containing 20 cc. of acetic acid and 20 cc. of 34% hydrobromic acid. At the end of this period, the hydrocarbon had crystallized from the boiling liquid. The mixture was cooled and the methylbenzanthracene collected. Once recrystallized from ethanol, it was obtained as yellow needles, m. p. 139–140° (cor.), and gave no depression of melting point when mixed with an authentic sample of 10-methyl-1,2-benzanthracene. The yield was 1.6 g. (86%), but a further quantity (0.19 g., m. p. 138–139°) could be obtained by concentration of the mother liquor.

Anal. Calcd. for $C_{19}H_{14}$: C, 94.18; H, 5.82. Found: C, 94.22; H, 5.96.

2-(*o*-Chlorobenzyl)-naphthalene.—A Grignard reagent was prepared in ether from 28.0 g. of β-iodonaphthalene and 2.7 g. of magnesium. An ether solution containing 14.4 g. of *o*-chlorobenzaldehyde was added and the mixture worked up as in the case of the isomer (I). The crude carbinol was reduced with red phosphorus and iodine, and the product distilled under reduced pressure. It was obtained as a nearly colorless oil, b. p. 203–204° (3 mm.); yield 7.9 g. (31%). This material was pure enough for further reaction, but could be separated from a small amount of high melting material (β,β'-dinaphthyl?) by addition of petroleum ether followed by cooling at 0° for twenty-four hours. The impurity crystallized and could be removed by filtration. Concentration of the filtrate followed by redistillation gave material of analytical purity.

Anal. Calcd. for $C_{17}H_{13}Cl$: C, 80.76; H, 5.19. Found: C, 80.89; H, 5.10.

In a single small scale experiment, starting from 9.1 g. of β-bromonaphthalene, the 2-naphthyl-(*o*-chlorophenyl)-methane was obtained in a yield of 3.5 g. (35%).

***o*-(2-Naphthylmethyl)-benzonitrile.**—A mixture of 20.2 g. of 2-(*o*-chlorobenzyl)-naphthalene, 9.0 g. of cuprous cyanide and 10 cc. of pyridine was heated for thirty hours at 250–260° and then worked up as in the case of the isomer (II). The product, b. p. 223–226° (3 mm.), solidified immediately on cooling; yield 11.1 g. (57%). This material was used without further purification in the following reaction, but could be crystallized from methanol as colorless prisms, m. p. 84.5–85.5°.

Anal. Calcd. for $C_{18}H_{13}N$: C, 88.85; H, 5.39. Found: C, 88.87; H, 5.01.

***o*-(2-Naphthylmethyl)-acetophenone** (V) was prepared from 9.75 g. of *o*-(2-naphthyl)-benzonitrile by the Grignard reaction in the same manner as that employed in the preparation of the isomer (III). Distilled under reduced pressure, it was obtained as a yellow, slightly fluorescent oil, b. p. 221° (3 mm.); yield 5.5 g. (52%).

Anal. Calcd. for $C_{19}H_{16}O$: C, 87.66; H, 6.19. Found: C, 87.82; H, 5.99.

9-Methyl-1,2-benzanthracene (VI).—Two grams of the ketone (V) obtained above was refluxed in a mixture of 20 cc. of acetic acid and 20 cc. of 34% hydrobromic acid. At the end of seventeen hours, the hydrocarbon solidified and after a total of twenty-four hours, refluxing was discontinued. Recrystallization of the material from methanol gave 1.6 g. (86%) of irregular, lemon-colored plates, m. p. 137.5–138.5° (cor.). This material gave no depression of melting point when mixed with an authentic specimen of 9-methyl-1,2-benzanthracene.

Anal. Calcd. for $C_{19}H_{14}$: C, 94.18; H, 5.82. Found: C, 94.00; H, 6.00.

Summary

Using a previously described method for the synthesis of *meso* substituted anthracene hydrocarbons, two carcinogenic compounds, 9-methyl- and 10-methyl-1,2-benzanthracene have been prepared.

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(5) All analyses by the Arlington Laboratories.