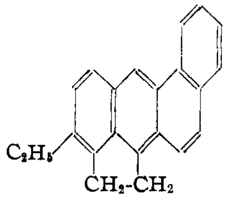
[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

Carcinogenic Hydrocarbons. II. Ethylcholanthrene[1]

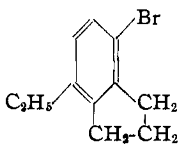
BY WILLIAM F. BRUCE AND SAMUEL J. KAHN

Since the study of homologous series has proved valuable for investigating a variety of physiologically active substances,[2] the preparation of a few members of the series which begins with cholanthrene and its 20-methyl derivative has been undertaken. The preparation of the 20-ethyl derivative (I) was accomplished in 1936,[3] but modifications in the general synthesis of Fieser and Seligman[4] introduced some unexpected complications which have required further study. In the meantime, Dr. M. J. Shear has found that 20-ethylcholanthrene gives rise to tumors when injected subcutaneously in mice but the average time of appearance (5 months) is twice that found for 20-methylcholanthrene. The 20-*t*-butyl derivative, which recently has been prepared,[5] appears to be still less active. The preparation of the 20-*n*-propyl and isopropyl cholanthrenes also has been undertaken, and will be reported in later papers.

By arrangement with Professor Fieser, the general synthesis of Fieser and Seligman[4] was used for the preparation of 20-ethylcholanthrene. The time for the Blanc reaction was reduced considerably in order to avoid the formation of a large quantity of tarry by-products. The saponification of the malonic esters by sodium hydroxide rather than barium hydroxide simplified the procedure and improved the yields. In our hands addition of the Grignard reagent, which was formed from the hydrindene (II), to α-naphthoyl chloride gave very poor yields of ketone (III) in this series. Other methods for preparing this substance were therefore investigated.



I



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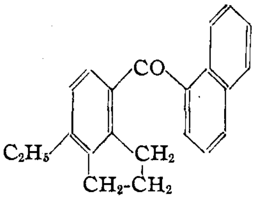
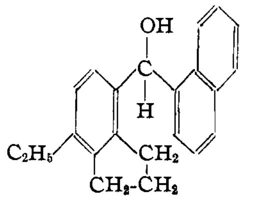
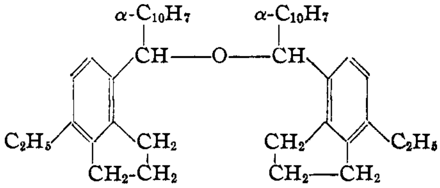


III



IV



V

The reaction between the Grignard reagent and α-naphthyl cyanide gave principally tarry materials from which no pure substance was isolated. The combination between the Grignard reagent and α-naphthaldehyde, however, gave a clean reaction. The carbinol (IV) which was isolated was treated with chromic acid in the presence of acetic and sulfuric acids, but the principal product, instead of being the expected ketone, appears from the analytical results to be the corresponding ether (V). This substance differs from both the carbinol and the ketone in its stability on standing exposed to air; it has retained its original pale yellow color but the carbinol and ketone have both become progressively darker. Upon pyrolysis this material gave 20-ethylcholanthrene in a yield comparable to that secured by pyrolysis of the ketone, which was subsequently prepared in another way.

In order to conduct a synthesis entirely parallel with respect to methods already established in this series, the hydrindene was converted to the nitrile,[4b] which with α-naphthylmagnesium bromide and hydrochloric acid gave the imine hydrochloride, readily converted to the ketone. Upon pyrolysis, the same substance was obtained as resulted from the previous series of reactions. 20-Ethylcholanthrene melts at 179.5–180° (corr.) and crystallizes from benzene or from *n*-propyl alcohol in small platelets, but not in the needle form often assumed by its homolog, 20-methylcholanthrene.

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(1) First Paper, Bruce with Fieser, THIS JOURNAL, **59**, 479–80 (1937).

(2) Dodds, *Lancet*, 987 (1934); Fieser, *et al.*, *Am. J. Cancer*, **29**, 266 (1937).

(3) Reported at the Pittsburgh meeting of the American Chemical Society.

(4) Fieser and Seligman, THIS JOURNAL, (a) **57**, 942 (1935); (b) **58**, 2482 (1936).

(5) Fieser and Snow, *ibid.*, **60**, 176 (1938).

Experimental Part

The Ethylbromobenzyl Chlorides.—To 450 g. of zinc chloride which was fused and cooled to 300° was added with stirring 4.5 g. of anhydrous aluminum chloride. The solid was rapidly pulverized while hot, since in this condition it is more friable and less hygroscopic, and was added to a mixture of 610 g. of *p*-bromoethylbenzene and 72.5 g. of trioxymethylene. The mixture was stirred vigorously[6] for eight hours at 40–50°. A slow stream of dry hydrogen chloride was passed into the mixture. At the end of the reaction hydrogen chloride was absorbed very slowly and the particles of zinc chloride were replaced by an oily complex. The mixture was worked up in the usual way.[4a] The product was fractionated to yield 234 g. of *p*-bromoethylbenzene and 360 g. (76%) of a mixture of chloromethyl derivatives boiling from 128–131° at 12 mm.

Anal.[7] Calcd. for $C_9H_{10}BrCl$: C, 46.28; H, 4.32. Found: C, 46.30; H, 4.36.

The residue (20 g.) solidified on cooling. By crystallization from benzene a substance was obtained in the form of large colorless needles melting at 83°, the dichloromethyl derivative.

Anal. Calcd. for $C_{10}H_{11}BrCl_2$: C, 42.55; H, 3.94. Found: C, 43.1; H, 4.09.

The Ethylbromobenzylmalonic Esters.—To a solution of 49 g. of sodium in 160 cc. of absolute alcohol, freshly distilled over sodium, was added 610 g. of ethyl malonate. After cooling the solution to 0°, 300 g. of the benzyl halide mixture was added. The reaction, conducted in the usual way,[4a] yielded a mixture of malonic esters boiling at 154° at 0.8 mm. for the lower boiling portion and 171–172° for the main portion. The yield was 334 g. (78%).

Anal. Calcd. for $C_{16}H_{21}O_4Br$: C, 53.78; H, 5.94. Found: C, 53.56; H, 5.93.

In addition a fraction (40 g.) boiling at 225–230° at 0.8 mm. was secured. This fraction is similar to that obtained at the corresponding stage in the synthesis of other members of the homologous series. The nature of these substances has not yet been studied other than to determine that they can be hydrolyzed to acids which do not decompose on melting.

The Ethylbromobenzylmalonic Acids.—A solution of 100 g. of sodium hydroxide in 450 cc. of water was added to a solution of 329 g. of the malonic ester mixture in 600 cc. of alcohol. The solution was boiled vigorously for four hours in an open flask on the steam-bath. Much of the alcohol evaporated during this time and the thick liquid was diluted with water to give a slightly turbid solution which was cooled and then acidified with 240 cc. of concentrated hydrochloric acid. The white precipitate which appeared was collected on a filter, washed thoroughly with water and dried. It weighed 236 g. (85%). A sample crystallized from acetic acid melted with decomposition at 165–166°.

Anal.[8] Calcd. for $C_{12}H_{13}O_4Br$: Br, 26.5. Found: Br, 26.0, 26.2.

The Ethylbromophenylpropionic Acids.—The malonic acids were converted to the propionic acids by heating the mixture at 165° until no more evolution of carbon dioxide occurred. The product was a thick viscous oil boiling from 156–160° at 1 mm.; yield 97%.

Anal. Calcd. for $C_{11}H_{13}O_2Br$: C, 51.36; H, 5.10. Found: C, 51.20; H, 5.28.

The Ethylbromohydrindones.—From 75 g. of the propionic acid mixture was obtained by the method of Fieser and Seligman[4a] 44 g. (74%) of the ethylbromohydrindones boiling from 166–168° at 14 mm. and melting at 77–78°.

Anal. Calcd. for $C_{11}H_{11}OBr$: C, 55.23; H, 4.64. Found: C, 54.90; H, 5.0.

4-Bromo-7-ethylhydrindene.—From 42 g. of the hydrindones was secured by Clemmensen reduction 35 g. of the hydrindene boiling at 145° at 17 mm. The distilled substance was further purified by washing with 80% sulfuric acid. The first washing was intensely red, the last nearly colorless. Upon redistillation 32 g. (80%) of the hydrindene resulted.

Anal. Calcd. for $C_{11}H_{13}Br$: C, 58.67; H, 5.82. Found: C, 58.77; H, 6.14.

Without purifying the intermediate stages, 300 g. of benzyl halide yielded 130 g. of pure hydrindene, an over-all yield of 45%.

4-Cyano-7-ethylhydrindene.[9]—From 32 g. of the hydrindene was obtained 12.3 g. (43%) of the cyanohydrindene boiling from 152–156° at 14 mm.

Anal. Calcd. for $C_{12}H_{13}N$: N, 8.2. Found: N, 8.5.

4-α-Naphthoyl-7-ethylhydrindene.[9]—The Grignard reagent prepared from 15 g. of α-bromonaphthalene converted 10 g. of the cyanohydrindene to the ketimine hydrochloride[4b] which decomposes at 216–218°.

Anal. Calcd. for $C_{22}H_{22}NCl$: N, 4.2. Found: N, 4.4.

By hydrolysis 12 g. of ketone resulted boiling from 205–210° at 0.5 mm.; yield 61%.

Anal. Calcd. for $C_{22}H_{20}O$: C, 87.9; H, 6.72. Found: C, 87.5; H, 7.01.

20-Ethylcholanthrene.—Pyrolysis of the ketone (10 g.) at 405–410° for one-half hour gave 2.7 g. (29%) of 20-ethylcholanthrene, melting at 161–163°. The product was crystallized from *n*-propyl alcohol and three times from benzene. The melting point, 179.5–180° (corr.), was unchanged during the last two crystallizations.

Anal. Calcd. for $C_{22}H_{18}$: C, 93.55; H, 6.45. Found: C, 93.8; H, 6.4.

α-Naphthyl-4-[7-ethylhydrindenyl]-carbinol.—To the Grignard reagent from 56.3 g. of the hydrindene was added at 0° 40 g. of α-naphthaldehyde in 500 cc. of absolute ether. After twelve hours the product was isolated in the usual way. It boiled from 222–225° at 1 mm. The yield was 28.3 g. (38%). The substance gives an intense purple color with concentrated sulfuric acid.

Anal. Calcd. for $C_{22}H_{22}O$: C, 87.37; H, 7.35. Found: C, 87.14; H, 7.09.

In addition, 9 g. of 4-ethylhydrindene, boiling at 125–

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[6] The stirrer consisted of a glass rod with a triangle at one end. Through the triangle were wound five three-inch (7-cm.) loops of number 18 nichrome wire; *cf.* Hershberg, *Ind. Eng. Chem., Anal. Ed.*, **8**, 312 (1936).

[7] Semi-micro analyses by W. G. Huckle.

[8] Analysis by E. B. Ashcraft.

[9] Prepared by R. G. Handrick.

130° at 43 mm. (71–72° at 2.5 mm.), was secured; yield 25%.

Anal. Calcd. for $C_{11}H_{14}$: C, 90.29; H, 9.64. Found: C, 90.13; H, 9.63.

Attempted Oxidation of the Carbinol.—To 8 g. of the carbinol in 20 cc. of glacial acetic acid was added slowly a solution of 2 g. of chromium trioxide in 3 cc. of water with 0.5 cc. of sulfuric acid. Heat was evolved and a green color was produced, but the temperature did not exceed 50°. The solution was shaken well for one-half hour, and was then poured into 200 cc. of water. The resulting mixture was extracted with four 50-cc. portions of benzene. The extract was washed with water and dilute sodium hydroxide. It was dried over calcium chloride and distilled. The product boiled at 225–230° at 1.5 mm. The yield was 6 g. (75%). In another experiment, similar treatment of 2 g. of carbinol gave 1.8 g. (90%) of the product. Larger quantities gave lower yields.

Anal. Calcd. for the ketone, $C_{22}H_{20}O$: C, 87.94; H, 6.72. Calcd. for the ether, $C_{44}H_{42}O$: C, 90.10; H, 7.22. Found: C, 90.19,[10] 90.51,[11] 90.47;[11] H, 7.26,[10] 7.55,[11] 7.6.[11]

Pyrolysis of the Ether.—From 1.8 g. of the above product, pyrolyzed at 410–415° for half an hour, was obtained 1.3 g. of crude hydrocarbon and when purified from benzene, 0.56 g. (33%) of ethylcholanthrene, melting at 179–180° (corr.).

Summary

20-Ethylcholanthrene has been synthesized by a general method previously developed by Fieser and Seligman. Some modifications of this procedure directed toward improving the yields and simplifying the operations for the preparation of this substance have been studied.

[10] Microanalysis by W. F. B.

[11] Microanalyses by Mrs. Verna R. Keevil, at Harvard University, by courtesy of Professor L. F. Fieser.

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Pyrolysis of Organomagnesium Compounds. I. A New Agent for the Reduction of Benzophenone

BY DANIEL B. CLAPP AND ROBERT B. WOODWARD

By the pyrolysis of ethylmagnesium bromide at 220°, *in vacuo*, a gas, which proved to be ethylene, was evolved, leaving a residual gray powder. The powder reacted vigorously with water, and with various alcohols, and sometimes caught fire in moist air. It possesses a peculiar, garlic-like odor, very similar to that observed with calcium hydride. The powder is practically insoluble in organic solvents with which it does not react.

By treatment of the pyrolysis product in suspension in an ether–benzene mixture with benzophenone, it has been possible to obtain a 66% yield of benzhydrol. No other products except unchanged benzophenone were isolated. This reduction of benzophenone cannot be due to any ethylmagnesium bromide which may be present in the pyrolysis product, since the gas evolved on hydrolysis of the product contains no ethane. Also, Noller and Hilmer[1] report that ethylmagnesium bromide reduces benzophenone only to the extent of 2%.

The composition of the pyrolysis product and the mode of its reducing action are being investigated. The product may well be similar to that obtained by Jolibois,[2] by the pyrolysis of ethylmagnesium iodide at 175° *in vacuo*. Jolibois claims that the following reaction takes place

$$2C_2H_5MgI \longrightarrow 2C_2H_4 + (2HMgI) \longrightarrow H_2Mg + MgI_2$$

The pyrolysis of methylmagnesium iodide was carried out like that of ethylmagnesium bromide. A product was obtained which was only slightly soluble in ether, indicating a reaction had taken place, but on treatment of this product with benzophenone, no benzhydrol could be isolated, and most of the benzophenone was recovered unchanged.

The pyrolysis of other organomagnesium compounds is being studied, and the reducing action of this new reagent with various classes of organic compounds is being investigated.

Experimental

Pyrolysis of Ethylmagnesium Bromide.—Ethylmagnesium bromide was prepared in the usual way from magnesium (8 g.) and ethyl bromide (36 g.). The Grignard solution was filtered under nitrogen through a sintered glass filter to remove any undissolved magnesium. The ether was removed according to the direction of Schoepfle and Trepp[3] for the preparation of ether-free phenylmag-

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[1] Noller and Hilmer, THIS JOURNAL, **54**, 2503 (1932).

[2] Jolibois, *Compt. rend.*, **155**, 353 (1912).

[3] Schoepfle and Trepp, THIS JOURNAL, **58**, 793 (1936).